Full Paper
doi.org/10.1002/ejoc.202000811

Triazole Amino Acids

Synthesis and Biological Evaluation of a Library of AGE-Related Amino Acid Triazole Crosslinkers

Esra Icik,[a] Anthony Jolly,[a] Paul Löffler,[a] Nektarios Agelidis,[a] Bakiye Bugdayci,[a] Luca Altevogt,[a,b] Ursula Bilitewski,[b] Angelika Baro,[a] and Sabine Laschat*[a]

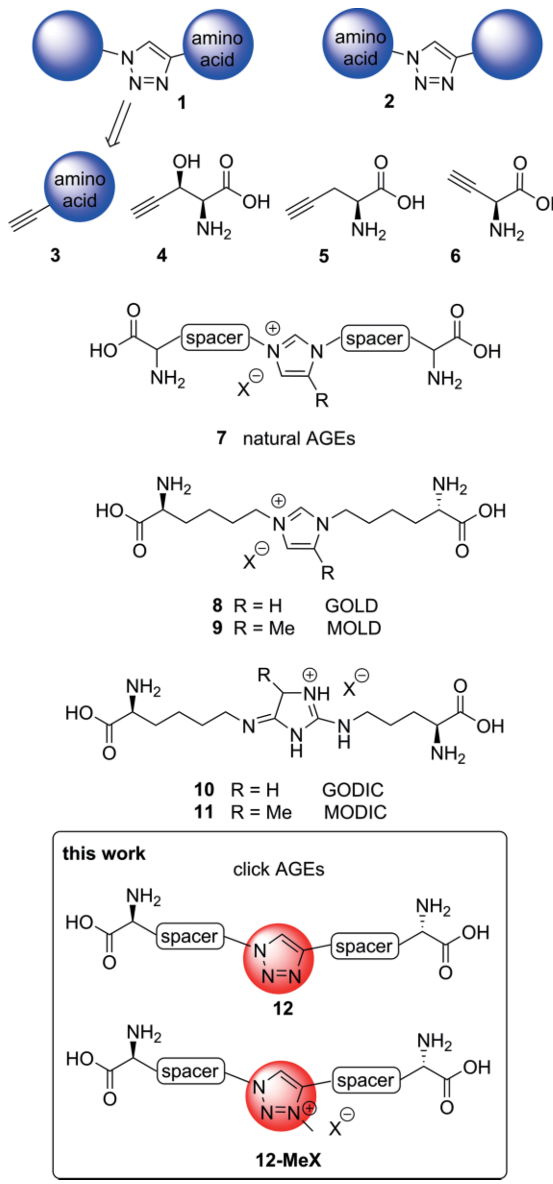
Abstract: Three *N*-Boc-protected amino acids, L-serine, L-aspartic, and L-glutamic acid, were either converted into their methyl azidoalkanoates or various alkynes via Bestmann-Ohira strategy or via reaction with propargylamine and propargyl bromide, respectively. The Cu-catalyzed click reaction provided a library of amino acid based triazoles, which were further *N*-methylated to triazolium iodides or deprotected and precipitated as free amino acid triazole dihydrochlorides. The biological properties of all derivatives were investigated by cytotoxicity assay (against L929 mouse fibroblasts) and broth microdilution method (*E. coli* ΔTolC and *S. aureus*). First results reveal complete inactivity for triazolium iodides with cell viabilities and microbial growths nearly 100 %, indicating them as possible analogs of advanced glycation endproducts (AGEs).

Introduction

Triazoles and in particular 1,2,3-triazoles are privileged scaffolds in both organic synthesis, material science, catalysis, chemical biology, and medicinal chemistry.[1a–1i] This is due to their convenient and convergent synthetic access from azides and alkynes via Cu-catalyzed 1,3-dipolar cycloaddition (i.e. click reaction) and Cu- or azide-free alternatives.[1e,1f] Furthermore, their possibility to form CH-π interactions to generate mesoionic carbenes makes them attractive as ligands to coordinate both metal ions as well as biological matter such as enzymes. In addition, the use of triazoles for the isosteric replacement of amides allows their use as pharmacophoric subunits in biologically active compounds and drugs.[1] The corresponding triazolium cations were employed as functional ionic liquids, precursors of mesoionic carbenes, and building blocks of supramolecular assemblies.[2] While various triazole containing amino acids and amino acid hybrid compounds **1**, **2** have been developed, e.g. for peptide drug conjugates, glycopeptides, peptide fluorescence labeling, and enzyme inhibitors,[3] dating back to 1996,[4] the crosslinking of peptides and proteins by bisamino acid triazoles has more recently received growing attention for tailored protein modifications, e.g. as β-turn mimetics and histidine isosters.[5] Moreover, the synthetic precursors of amino acid triazoles, i.e. the alkynylamino acids **3** are highly interesting compounds themselves, because they are not only building blocks for click chemistry[3,5,6,7] and Sonogashira cross-coupling for the synthesis of desmosine, isodesmosine and related heterocyclic cationic crosslinkers of connective tissue proteins, but also biosynthetic intermediates.[8] Very recently, the biosynthetic pathway of amino acids containing terminal alkynes, e.g. L-ethynylserine **4**, propargylglycine **5**, and ethynylglycine **6** were discovered in the bacterium *Streptomyces cattleya* (Scheme 1).[9] Besides the many histidine-containing peptides, crosslinking amino acids and peptides carrying imidazole and imidazolium units have also received much interest. For example, glyoxallysine dimer (GOLD) **8**, methylglyoxal-lysine dimer (MOLD) **9**, glyoxal- and methylglyoxal-derived imidazolium crosslinks (GODIC, MODIC) **10**, **11** and other more complex structures have been extensively investigated.[10–14] These compounds are members of a large class of advanced glycation endproducts (AGEs) **7**, which are biosynthetically formed by the Maillard reaction of proteins and carbohydrates that result in protein crosslinking. From a biological point of view, AGEs play an important role in such diverse areas as browning and processing of food[11] as well as aging of tissue and protein-degenerative diseases, associated with diabetes.[15]

Natural imidazolium-based AGEs are useful medical markers but often difficult to synthesize.[13] Therefore, we anticipated that synthetic AGEs carrying a triazolium core instead of the imidazolium unit might be a promising alternative, because they should be readily available by Cu-catalyzed click reaction of amino acid-derived alkynes and azides, respectively.[1h] It was therefore our aim to provide a library of AGE analogs, carrying a central triazole **12** or triazolium unit **12-MeX** rather than an

[a] E. Icik, A. Jolly, P. Löffler, N. Agelidis, B. Bugdayci, L. Altevogt, Dr. A. Baro, Prof. S. Laschat
Institut für Organische Chemie, Universität Stuttgart,
Pfaffenwaldring 55, 70569 Stuttgart, Germany
E-mail: sabine.laschat@oc.uni-stuttgart.de
https://www.ioc.uni-stuttgart.de/en/research/ak-laschat/
[b] L. Altevogt, Prof. U. Bilitewski
AG Compound Profiling and Screening, Helmholtz Zentrum für Infektionsforschung,
Inhoffenstr. 7, 38124 Braunschweig, Germany
E-mail: ursula.bilitewski@helmholtz-hzi.de
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202000811.

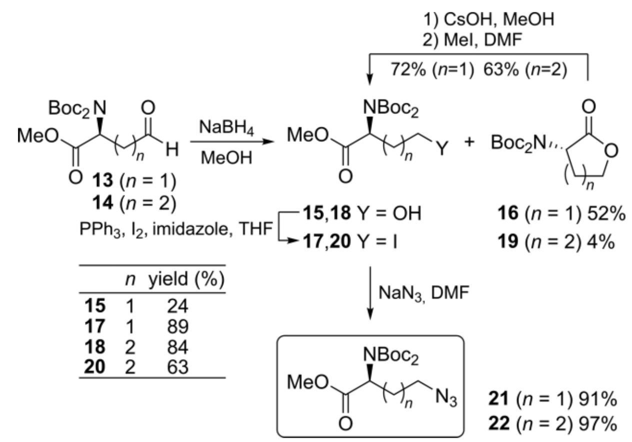


Scheme 1.

imidazolium unit. Moreover, the possibility for *N*-alkylation enables the comparison of charged and neutral crosslinkers and broadens the scope regarding structure-activity relationship (SAR) studies. The realization of these "click AGEs" and their preliminary biological investigation are discussed in the current manuscript.

Results and Discussion

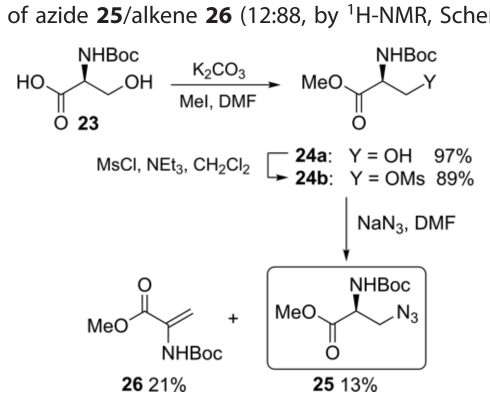
The synthesis of azides **21** and **22** derived from L-aspartic acid and L-glutamic acid is shown in Scheme 2. The starting aldehydes **13** and **14** were accessible in three steps from the respective amino acids.[16] When aldehyde **13** was treated with $NaBH_4$ according to the method by Adamczyk,[17] alcohol **15** was isolated in only 24 % besides 52 % of the undesired δ-lactone **16**. Fortunately, the latter could be converted to alcohol **15** by treatment with CsOH in MeOH followed by reaction with MeI in DMF in 72 %.[18] Subsequent iodination under Appel conditions[17,19] and nucleophilic displacement with NaN_3 in DMF[20] yielded azide **21** in 81 % over two steps.



Scheme 2.

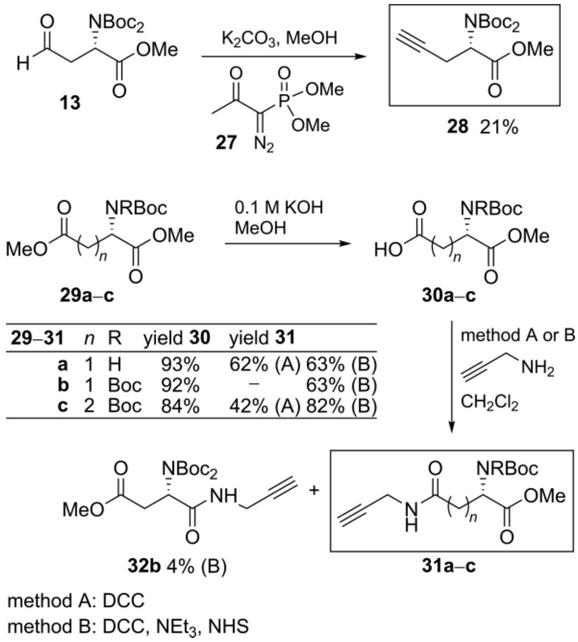
In a similar fashion $NaBH_4$ reduction of aldehyde **14** gave alcohol **18** in 84 % yield and was accompanied by lactone **19** formation (4 %). Lactone **19** could be recycled to **18** in 63 %. Alcohol **18** was then converted in two steps into azide **22** in 72 % (over two steps). **18** was also converted into a mesylate and treated with NaN_3[21] to obtain azide **22** (Scheme S2).

The synthesis of L-serine-derived azide **25** commenced with *N*-Boc-serine methyl ester **24a**, which was available in two steps from L-serine via *N*-Boc-serine **23** in 97 % (Scheme 3).[22] Methyl ester **24a** was converted into the mesylate **24b**[23] in 89 % followed by treatment with NaN_3 according to a method by Shetty.[23] In agreement with previous work by Meffre[24] under these conditions the desired azide **25** was obtained in 13 % yield together with 21 % of alkene **26**, which resulted from an elimination reaction. The alternative route via Appel reaction according to a method by Fenster[17,25] gave the respective iodide in a disappointingly low yield of 26 % and was accompanied by alkene **26** (4 %) (Scheme S3). When the iodide was submitted to the S_N2 reaction with NaN_3 following a method by Roth,[20] the elimination by-product dominated, giving a crude mixture of azide **25**/alkene **26** (12:88, by ^{1}H-NMR, Scheme S3).

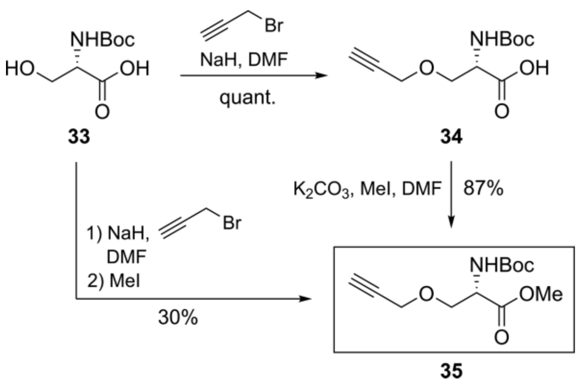


Scheme 3.

The syntheses of amino acid alkynes are summarized in Scheme 4 and Scheme 5. Aspartate-derived propargylglycine **28** was prepared from aldehyde **13** in 21 % yield via the Bestmann-Ohira strategy[24,26] utilizing β-keto-diazophosphonate **27**[24,27] for one-carbon homologation and K_2CO_3 as a base[23] (Scheme 4).



Scheme 4.



Scheme 5.

The synthesis of amino acid alkynes **31** commenced with saponification of known dimethyl esters **29**[16,28] with KOH in MeOH to the respective monomethyl esters **30**. The reaction of **30** with propargylamine was performed using method A or B (Scheme 4). Alkyne **31a** was isolated by both methods in comparable yields of 62 and 63 %. When mono ester **30b** was treated with propargylamine in the presence of DCC and *N*-hydroxysuccinimide (NHS)[29] (method B, Scheme 4), ω-propargylamide **31b** was obtained in 63 % together with 4 % of the α-propargylamide **32b**. In the case of monoester **30c**, however, the yield of ω-propargylamide **31c** could be significantly improved from 42 % (method A, Scheme 4)[30] to 82 % by addition of NEt_3 and NHS.

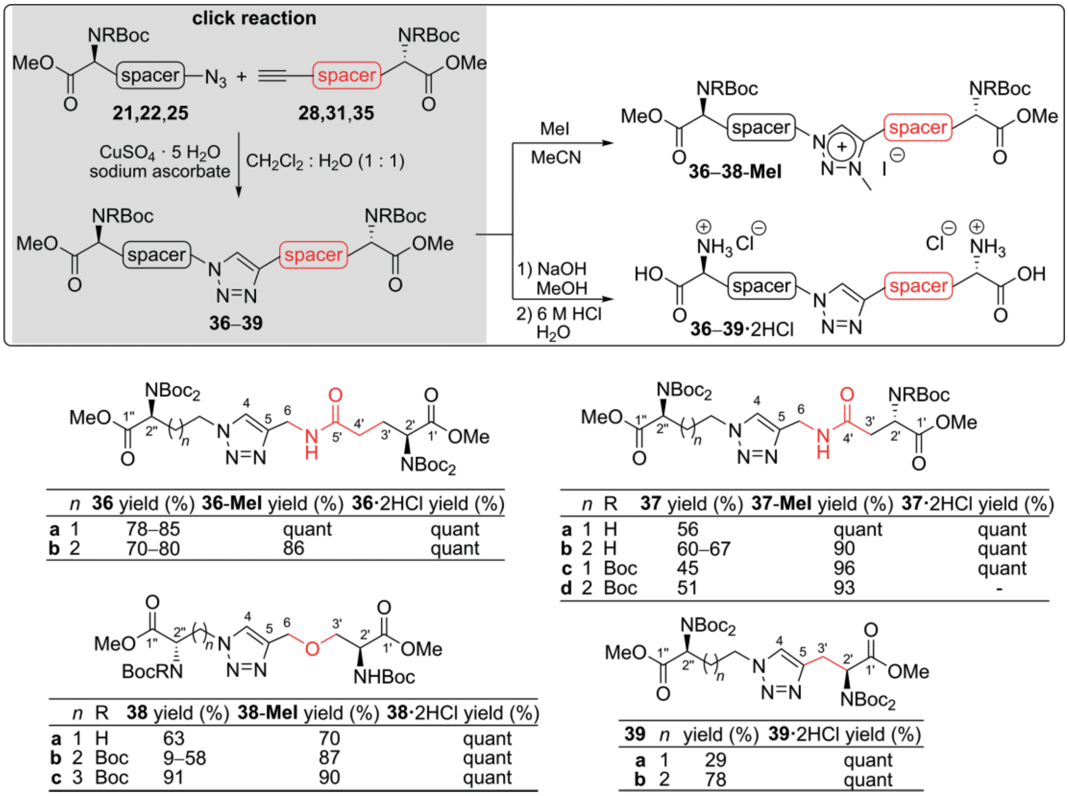
As shown in Scheme 5, serine propargyl ether **35** was synthesized starting from *N*-Boc serine **33** by Williamson etherification with propargyl bromide and NaH[31] to give acid **34** quantitatively. The latter was then esterified yielding the desired alkyne **35** in 87 %.[22] When the intermediate free acid **34** was not isolated and the two-step reaction was carried out in one pot,[32] the yield of **35** decreased to 30 %. However, by switching the sequence of Williamson etherification and esterification, no trace of propargyl ether **35** was detected.

With the azides **21**, **22**, **25** and alkynes **28**, **31**, **35** in hand, the Cu-catalyzed 1,3-dipolar cycloaddition was investigated (Scheme 6).[33,34] After some optimization (for details see Table S1, Supporting Information), azides **21**, **22**, **25** and alkynes **28**, **31**, **35** were treated with 2 mol-% $CuSO_4{\cdot}5H_2O$, 20 mol-% sodium ascorbate in CH_2Cl_2/H_2O (1:1) for 2–5 days at room temperature to obtain a library of triazoles **36**–**39** (Scheme 6).

Under these conditions, the aspartic acid-derived azide **21** and the alkyne **31a** reacted to triazole **37a** in 56 %. Click reaction of **21** and **31b** gave the di-*N*-Boc-protected counterpart **37c** in 45 % yield. Triazoles **37b**,**d** obtained from azide **22** and alkynes **31a**,**b** were isolated in similar yields. Compared to the di-*N*-Boc triazoles **37c**,**d** based on aspartic acid derived alkyne **31b** the corresponding glutamic acid derived alkyne **31c** gave the triazoles **36a,b** in higher yields up to 85 %. In the click reaction between serine-based alkyne **35** and the series of azides, the glutamic acid-derived **22** gave the highest yield of 91 % for triazole **38c**. The lowest yield was obtained for **38b** (9–58 %). Using *t*BuOH as a solvent for the formation of **38b** resulted in low yields (Scheme S1). Yields of triazoles **39** ranged between 29 % for the aspartate-serine-derived click product **39a** and 78 % for the glutamate-serine-derived triazole **39b**. Subsequent deprotection[35] of the triazoles **36**–**38** was achieved with NaOH in MeOH, followed by treatment with 6 N HCl in H_2O to give the free bisamino acid triazole bishydrochlorides **36**–**39**•2HCl in quantitative yield (Scheme 6). Compounds **36**–**39**•2HCl precipitated with 2–3 equiv. of NaCl. Aqueous solutions of **36**–**39**•2HCl have acidic pH-values approving the bishydrochlorides. In addition, protected triazoles **36**–**38** were *N*-alkylated with MeI in MeCN to give the *N*-methyl-triazolium iodides **36-MeI** – **38-MeI** in 70 % to quantitative yield.[36]

Next, the biological properties of the click products were investigated using the single concentration of 100 μM in the primary assay. Both protected and unprotected triazole bisamino acids **36**–**39**, **36**–**39**•2HCl as well as the protected triazolium iodides **36**-**MeI** – **38**-**MeI** were submitted to a standard Alamar Blue cytotoxicity assay[37] against the L929 mouse fibroblast cell line. In addition, antimicrobial activities against the Gram-negative bacterium *Escherichia coli* ΔTolC and the Gram-positive bacterium *Staphylococcus aureus* were examined by measuring %growth via the broth microdilution method. The results in Table S2 revealed some general trends. Irrespective of the amino acid residues the unprotected triazole bisamino acids **36**–**39**•2HCl were weakly cytotoxic, showing cell viabilities of 50–61 %. However, no antimicrobial activities were observed. Similar results were found for the *N*-Boc-protected triazole bisamino acid methyl ester **36**–**39**. In contrast, the protected triazolium iodides **36**-**MeI** – **38**-**MeI** were completely inactive in both tests. In other words, for this series the cell viabilities and antimicrobial growths were close to 100 %. Presumably, the triazolium moiety seems to promote cell compatibility for both

doi.org/10.1002/ejoc.202000811



	n	**36** yield (%)	**36-MeI** yield (%)	**36**·2HCl yield (%)
a	1	78–85	quant	quant
b	2	70–80	86	quant

	n	R	**37** yield (%)	**37-MeI** yield (%)	**37**·2HCl yield (%)
a	1	H	56	quant	quant
b	2	H	60–67	90	quant
c	1	Boc	45	96	quant
d	2	Boc	51	93	-

	n	R	**38** yield (%)	**38-MeI** yield (%)	**38**·2HCl yield (%)
a	1	H	63	70	quant
b	2	Boc	9–58	87	quant
c	3	Boc	91	90	quant

39	*n*	yield (%)	**39**·2HCl yield (%)
a	1	29	quant
b	2	78	quant

Scheme 6.

eukaryotic and prokaryotic cells. It should be emphasized that the absence of cytotoxicity for triazolium salts is in a good agreement with a recent comparative SAR study on triazoles and triazolium salts by da Silva.[38]

Conclusion

In the current work, a library of triazole bisamino acids has been synthesized via Cu-catalyzed click reaction from serine-, glutamic acid- and aspartic acid-derived azides and the corresponding alkynes. The azides based on aspartic and glutamic acid were synthesized with yields of 14–49 % over 6 steps. Thereby lactone formations were not avoidable, but ring-opening reactions were performed. The alkynes also based on these two amino acids were obtained in 15–61 % yields over 4–5 steps by Bestmann-Ohira strategy and amidation reactions. The serine derived azide was isolated over 3 steps in low yields of 3–11 %. However, the serine derived alkyne was synthesized with a high yield of 87 % performing a Williamson etherification and esterification. Methylation of the *N*-Boc-protected triazole amino acid methyl esters provided the corresponding triazolium iodides. According to preliminary biological studies fully protected triazole bisamino acids **36**–**39** were weakly cytotoxic, whereas the corresponding triazolium iodides **36-MeI** – **38-MeI** did not show cytotoxic or antimicrobial activity, which makes them suitable to study their potential as click AGE mimics without interfering cytotoxic or antimicrobial activity. Work towards this goal is in progress.

Experimental Section

General: NMR spectra were recorded on Bruker Avance 300, 400, 500, and 700 MHz instruments. The chemical shifts (δ) are given in ppm and were referenced to residual solvent signal. The signals were assigned by using additional HSQC-, COSY- and HMBC experiments. For easier comparison of NMR spectra, atom numbering may deviate from the IUPAC nomenclature. IR spectra were recorded on a Bruker FT-IR spectrometer ALPHA equipped with a diamond ATR system (*Platinum ATR*) or a Bruker Vector 22 with MKII Golden Gate Single Reflection Diamant ATR system. HRMS spectra were measured on a Bruker micrOTOF-Q spectrometer via electrospray ionization (ESI). Melting points were measured on a Stuart SMP10 apparatus. Column chromatography was performed using silica gel 60 M (Macherey-Nagel, grain size 40–63 µm). All chemicals were used as purchased unless otherwise stated. CH_2Cl_2 and NEt_3 were dried with CaH_2 by heating at reflux and subsequent distillation, THF was dried with potassium with benzophenone as an indicator. Hexanes (b.p. 30–70 °C), EtOAc, CH_2Cl_2, and MeOH for chromatography were distilled prior to use. Moisture sensitive reactions were performed in oven-dried glassware under N_2 atmosphere. Methyl (2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-4-azidobutanoate (**21**),[20] methyl (2*S*)-2-(*tert*-butoxycarbonyl)amino-3-azidopropanoate (**25**),[20] methyl (2S)-2-[bis(*tert*-butoxycarbonyl)amino]-pent-4-ynoate (**28**),[24] methyl N^2-(*tert*-butoxycarbonyl)-N^4-prop-2-ynyl-L-α-asparaginate (**31a**),[29,30] and methyl *N*-(*tert*-butoxycarbonyl)-O-prop-2-ynyl-L-serinate (**35**)[22,32] were synthesized following the literature (see SI).

Methyl (2*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-5-azidopentanoate (22): According to ref.[20] iodide **20** (2.61 g, 5.71 mmol) and NaN_3 (0.75 g, 11.5 mmol) were dissolved in DMF (27 mL). The reaction mixture was heated under reflux at 40 °C for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (30 mL). After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 8:1) to afford **22** (2.05 g, 5.52 mmol, 97 %) as a colorless oil. $[\alpha]_D^{20}$ = –38.92 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 [s, 18H; C(CH_3)$_3$], 1.60–1.75 (m, 2H; 3-H_α, 4-H_α), 1.90–2.02 (m, 1H; 4-H_β), 2.14–2.26 (m, 1H; 3-H_β), 3.24–3.39 (m, 2H; 5-H), 3.72 (s, 3H; 1-OMe), 4.86 ppm (dd, *J* = 9.4 Hz, 5.3 Hz, 1H; 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7 (C-4), 27.2 (C-3), 28.0 [2 × C(CH_3)$_3$], 51.0 (C-5), 52.2 (1-OMe), 57.6 (C-2), 83.3 [2 × *C*(CH_3)$_3$], 152.1 (2 × *C*OO*t*Bu), 171.0 ppm (C-1); FT-IR (ATR): $\tilde{\nu}$ = 2979 (m, br), 2936 (m, br), 2096 (s), 1795 (w), 1746 (vs), 1699 (s), 1456 (w, br), 1367 (s), 1311 (m), 1250 (s, br), 1169 (s), 1144 (vs), 1012 (w, br), 900 (w), 855 (w), 812 (w), 782 (w, br), 667 (w), 464 (w) cm^{-1}; MS (ESI): *m/z* = 395 [*M* + Na]$^+$, 295 [*M*-Boc + Na]$^+$, 239 [*M* – *tert*-butyl + Na]$^+$, 195 [*M*-2 × Boc + Na]$^+$, 173; HRMS (ESI): *m/z* calcd. for $C_{16}H_{28}N_4O_6Na^+$: 395.1901 [*M* + Na]$^+$, found 395.1892.

Methyl *N*^{2},*N*^{2}-Bis(*tert*-butoxycarbonyl)-*N*^{4}-prop-2-ynyl-L-α-asparaginate (31b): According to ref.[29] under N_2-atmosphere **30b** (2.03 g, 5.84 mmol) was dissolved in CH_2Cl_2 (203 mL) and cooled to 0 °C. NHS (1.49 g, 12.9 mmol) and DCC (2.70 g, 13.1 mmol) were added and stirred for 15 min. NEt_3 (1.8 mL, 1.31 g, 13.0 mmol) and propargylamine (0.81 mL, 0.70 g, 12.6 mmol) was added and stirred for 1 d at r.t. The solution was filtered off and washed with 0.1 M H_2SO_4 solution (4 × 100 mL), H_2O (2 × 200 mL), and saturated $NaHCO_3$ solution (2 × 200 mL). The organic phase was dried with $MgSO_4$ and filtered off. After evaporation of the solvent, EtOAc was added to the residue and cooled to –15 °C and filtered off. The solvent was removed under reduced pressure and purified by column chromatography on silica gel (hexanes/EtOAc, 3:1) to afford **31b** (1.86 g, 4.84 mmol, 63 %) as a colorless oil. R_f = 0.25 (hexanes/EtOAc, 3:1); $[\alpha]_D^{20}$ = –41.8 (*c* = 1.47 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 [s, 18H; 2 × C(CH_3)$_3$], 2.22 (t, *J* = 2.6 Hz, 1H; 3′-H), 2.62 (dd, *J* = 15.2, 6.1 Hz, 1H; 3-H_a), 3.11 (dd, *J* = 15.2, 7.3 Hz, 1H; 3-H_b), 3.72 (s, 3H; OMe), 4.02–4.08 (m, 2H; 1′-H), 5.45 (t, *J* = 6.7 Hz, 1H; 2-H), 5.93 ppm (brs, 1H; N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [2 × C(CH_3)$_3$], 29.5 (C-1′), 38.1 (C-3), 52.7 (OMe), 55.4 (C-2), 71.8 (C-3′), 79.6 (C-2′), 83.7 [2 × *C*(CH_3)$_3$], 152.0 (2 × *C*OO*t*Bu), 169.4 (C-1), 170.9 ppm (C-4); FT-IR (ATR): $\tilde{\nu}$ = 568 (w), 666 (w), 779 (w), 852 (m), 928 (w), 10001 (w), 1059 (w), 1116.3 (s), 1143 (vs), 1231 (s), 1274 (s), 1312 (s), 1368 (vs), 1437 (m), 1457 (m), 1540 (m), 1700 (s), 1747 (vs), 1787 (m), 2853 (w), 2932 (m), 2980 (m), 3299 (br, m) cm^{-1}; MS (ESI): *m/z* = 431, 407 [*M* + Na]$^+$, 385, 329, 307, 285, 251, 229, 207, 185, 125; HRMS (ESI): *m/z* calcd. for $C_{18}H_{28}N_2O_7Na^+$: 407.1789 [*M* + Na]$^+$, found 407.1777.

As a side product methyl (3*S*)-3-[bis(*tert*-butoxycarbonyl)amino]-1-prop-2′-ynylamido-butanoate **32b** (87.0 mg, 0.23 mmol, 4 %) was obtained as a white solid. M.p. 143 °C; R_f = 0.47 (hexanes/EtOAc, 3:1); $[\alpha]_D^{20}$ = –42.8 (*c* = 1.07 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 [s, 18H; 2 × C(CH_3)$_3$], 2.21 (t, *J* = 2.5 Hz, 1H; 3′-H), 2.77 (dd, *J* = 16.7, 6.9 Hz, 1H; 3-H_a), 3.33 (dd, *J* = 16.7, 6.5 Hz, 1H; 3-H_b), 3.69 (s, 3H; OMe), 3.95–4.04 (m, 1H; 1′-H_a), 4.07–4.16 (m, 1H; 1′-H_b), 5.19 (t, *J* = 6.8 Hz, 1H; 2-H), 6.09–6.16 ppm (m, 1H; N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [2 × C(CH_3)$_3$], 29.6 (C-1′), 35.2 (C-3), 52.1 (OMe), 56.2 (C-2), 72.0 (C-3′), 79.4 (C-2′), 84.3 [2 × *C*(CH_3)$_3$], 151.9 (2 × *C*OO*t*Bu), 169.0 (C-1), 171.8 ppm (C-4); FT-IR (ATR): $\tilde{\nu}$ = 411 (w), 659 (w), 778 (w), 813 (w), 852 (m), 931 (w), 973 (w), 1027 (w), 1117 (s), 1140 (vs), 1166 (s), 1236 (s), 1307 (s), 1369 (s), 1438 (m), 1457 (m), 1479 (m), 1521 (m), 1698 (s), 1739 (vs), 1790 (m), 2933 (m), 2980 (m), 3279 (br, w) cm^{-1}; MS (ESI): *m/z* = 449, 431, 407 [*M* + Na]$^+$, 385, 349, 307, 285, 251, 229, 207, 185, 167, 153; HRMS (ESI): *m/z* calcd. for $C_{18}H_{28}N_2O_7Na^+$: 407.1789 [*M* + Na]$^+$, found 407.1786.

Methyl *N*^{2},*N*^{2}-Bis(*tert*-butoxycarbonyl)-*N*^{4}-prop-2-ynyl-L-α-glutaminate (31c): Method B: According to ref.[29] under N_2-atmosphere **30c** (203 mg, 0.56 mmol) was dissolved in anhydrous CH_2Cl_2 (21 mL) and cooled to 0 °C. Then NHS (157 mg, 1.36 mmol) and DCC (254 mg, 1.23 mmol) were added to the cooled solution and stirred for 15 min. After adding NEt_3 (0.18 mL, 131 mg, 1.30 mmol) and propargylamine (0.08 mL, 69 mg, 1.25 mmol), the reaction was stirred for 1 d at r.t. The reaction mixture was filtered off and washed with 0.1 M H_2SO_4 solution (2 × 40 mL), H_2O (2 × 60 mL), and saturated $NaHCO_3$ solution (2 × 40 mL). The organic phase was dried with $MgSO_4$ and filtered off. After removing the solvent, the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 3:1, phosphomolybdic acid), to afford **31c** (182 mg, 0.46 mmol, 82 %) as a white solid.

Method A: According to ref.[30] under N_2-atmosphere **30c** (118 mg, 0.33 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) and cooled to 0 °C. Then DCC (72.0 mg, 0.35 mmol) and propargylamine (0.03 mL, 25.8 mg, 0.47 mmol) were added to the cooled solution and stirred for 1 d at r.t. The reaction solution was filtered off and the solvent was removed. The residue was taken up in EtOAc and filtered off again. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 3:1) to afford **31c** (54.0 mg, 0.14 mmol, 42 %) as a white solid. M.p. 119 °C; R_f = 0.19 (hexanes/EtOAc, 3:1);] $[\alpha]_D^{20}$ = –29.0 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 [s, 18H; 2 × C(CH_3)$_3$], 2.13–2.21 (m, 1H; 3-H_a), 2.22 (t, *J* = 2.6 Hz, 1H; 3′-H), 2.30 (t, *J* = 7.5 Hz, 2H; 4-H), 2.44–2.56 (m, 1H; 3-H_b), 3.72 (s, 3H; OMe), 4.02–4.07 (m, 2H; 1′-H), 4.88 (dd, *J* = 8.9, 5.4 Hz, 1H; 2-H), 5.75–5.84 ppm (m, 1H; N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (C-3), 28.1 [C(CH_3)$_3$], 29.4 (C-1′), 33.0 (C-4), 52.3 (OMe), 57.9 (C-2), 71.8 (C-3′), 79.7 (C-2′), 83.8 [*C*(CH_3)$_3$], 152.3 (*C*OO*t*Bu), 171.0 (C-1), 171.6 ppm (C-1); FT-IR (ATR): $\tilde{\nu}$ = 465 (w), 665 (br, m), 785 (m), 853 (m), 1035 (m), 1116 (vs), 1140 (vs), 1168 (s), 1247 (s), 1312 (s), 1368 (vs), 1456 (m), 1535 (m), 1655 (s), 1700 (s), 1743 (vs), 1785 (m), 2980 (m), 3284 (br, m) cm^{-1}. MS (ESI): *m/z* = 421 [*M* + Na]$^+$, 399, 343, 321, 299, 266, 243, 221, 199, 182, 166, 144; HRMS (ESI): *m/z* calcd. for $C_{19}H_{30}N_2O_7Na^+$: 421.1945 [M + Na]$^+$, found 421.1938.

General Procedure for the Click Reaction: According to ref.[33,34] azides **21**, **22**, **25** (1.00 mmol) and alkynes **28**, **31**, **35** (1.00 mmol) were dissolved in water (10 mL) and CH_2Cl_2 (10 mL). $CuSO_4$•5H_2O (0.01–0.02 mmol) and sodium ascorbate (0.1–0.2 mmol) were added. After stirring the reaction for several hours, one or two more times $CuSO_4$•5H_2O (0.01–0.02 mmol) and sodium ascorbate (0.1–0.2 mmol) were added depending on the conversion shown on the TLC and stirred for another certain time at r.t. After adding CH_2Cl_2 (30 mL), the aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, and filtered off. After evaporation of the solvent, the residue was purified by column chromatography on silica gel. Due to the high viscosity of the click-products removal of the solvent by lyophilization was difficult, so spectra contain 3–29 % of EtOAc.

5-((1-((*S*)-4-(Methyloxy)-3-((Bis(*tert*-butoxycarbonyl)amino))-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(Bis(*tert*-butoxycarbonylamino))-amidopentyl-methyl Ester (36a): From the azide **21** (46.0 mg, 0.13 mmol) and alkyne **31c** (45.0 mg, 0.11 mmol) in water (0.90 mL) and CH_2Cl_2 (0.90 mL), $CuSO_4$•5H_2O (1.23 mg, 4.93 μmol) and sodium ascorbate (8.52 mg, 43.0 μmol), 22 h; $CuSO_4$•5H_2O (2.42 mg, 9.69 μmol) and sodium ascorbate (8.71 mg, 44.0 μmol), 22 h, **36a** (72.0 mg, 95.1 μmol, 85 %), colorless oil. R_f = 0.13 (hexanes/EtOAc, 1:2); $[\alpha]_D^{20}$ = –14.8 (*c* = 0.86 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [s, 18H; 2 × C(CH_3)$_3$], 1.49 [s, 18H; 2 ×

C(CH_3)$_3$], 2.12–2.24 (m, 1H, 3′′-H$_a$), 2.28 (t, *J* = 7.2 Hz, 2H; 4′-H), 2.39–2.59 (m, 2H; 3′′-H$_b$, 3′-H$_a$), 2.75–2.86 (m, 1H; 3′-H$_b$), 3.71 (s, 3H; OMe), 3.73 (s, 3H; OMe), 4.37–4.60 (m, 4H; 4′′-H, 6-H), 4.82–4.96 (m, 2H; 2′-H, 2′′-H), 6.25–6.33 (m, 1H; N*H*), 7.62 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 25.8 (C-3′′), 28.1 [4 × C(CH_3)$_3$], 31.0 (C-3′), 32.9 (C-4′), 34.6 (C-6), 48.3 (C-4′′), 52.3, 52.6 (OMe), 55.6, 57.7 (C-2′, C-2′′), 83.5, 84.0 [4 × *C*(CH$_3$)$_3$], 123.4 (C-5), 144.2 (C-4), 152.1, 152.2 [4 × *C*OO*t*Bu], 170.3, 171.0, 172.2 ppm (C-1′, C-5′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 413 (w), 461 (w), 647 (w), 665 (w), 731 (m), 782 (m), 853 (m), 913 (w), 1013 (m), 1049 (m), 1141 (vs), 1166 (s), 1232 (s), 1367 (vs), 1437 (m), 1456 (m), 1529 (m), 1700(s), 1744 (vs), 1789 (m), 2035 (w), 2054 (w), 2115 (w), 2151 (w), 2185 (w), 2201 (w), 2266 (w), 2980 (m), 3366 (br w) cm^{-1}; MS (ESI): *m/z* = 795, 779 [*M* + Na]$^+$, 757, 695, 679, 657, 595, 579, 557, 523, 501, 457, 439, 401, 383, 357; HRMS (ESI): *m/z* calcd. for $C_{34}H_{56}N_6O_{13}Na^+$: 779.3798 [*M* + Na]$^+$, found 779.3787.

5-((1-((*S*)-5-(Methyloxy)-4-((Bis(*tert*-butoxycarbonyl)amino))-5-oxopentyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(Bis(*tert*-butoxycarbonylamino))-amidopentyl-methyl Ester (36b): From the azide **22** (97.0 mg, 0.26 mmol) and the alkyne **31c** (100 mg, 0.25 mmol) in water (1.50 mL) and CH$_2$Cl$_2$ (1.50 mL), CuSO$_4$•5H$_2$O (2.00 mg, 8.01 µmol) and sodium ascorbate (11.6 mg, 58.6 µmol), 3 d, CuSO$_4$•5H$_2$O (1.15 mg, 4.61 µmol) and sodium ascorbate (7.07 mg, 35.7 µmol), 6 h, CuSO$_4$•5H$_2$O (1.00 mg, 4.00 µmol) and sodium ascorbate (5.30 mg, 26.7 µmol), 18 h, **36b** (151 mg, 0.20 mmol, 80 %) as a colorless oil. R_f = 0.16 (hexanes/EtOAc, 1:2); $[\alpha]_D^{20}$ = –33.1 (*c* = 0.71 in CH$_2$Cl$_2$); ^{1}H NMR (700 MHz, CDCl$_3$): δ = 1.48 [s, 36H; 4 × C(CH_3)$_3$], 1.86–1.95 (m, 1H; 3′′-H$_a$), 1.96–2.04 (m, 2H; 4′′-H), 2.09–2.23 (m, 2H; 3′′-H$_b$, 3′-H$_a$), 2.26–2.31 (m, 2H; 4′-H), 2.45–2.52 (m, 1H; 3′-H$_b$), 3.71 (s, 6H; 2 × OMe), 4.40 (t, 2H; 5′′-H), 4.48–4.59 (m, 2H; 6-H), 4.85–4.91 (m, 2H; 2′-H, 2′′-H), 6.38 (s, 1H; N*H*), 7.63 ppm (s, 1H; 5-H); ^{13}C NMR (175 MHz, CDCl$_3$): δ = 25.8 (C-3′), 27.1 (C-3′′, C-4′′), 28.1 [4 × C(CH_3)$_3$], 32.9 (C-4′), 34.8 (C-6), 50.4 (C-5′′), 52.4, 52.5 (2 × OMe), 57.3, 57.7 (C-2′, C-2′′), 83.5, 83.7 [*C*(CH$_3$)$_3$], 123.0 (C-5), 144.2 (C-4), 152.2 (4 × *C*OO*t*Bu), 170.9, 171.0, 172.1 ppm (C-1′, C-5′, C-1′′). FT-IR (ATR): $\tilde{\nu}$ = 416 (w), 459 (w), 784 (m), 854 (m), 1142 (vs), 1168 (s), 1250 (s), 1313 (m), 1368 (vs), 1457 (m), 1530 (m), 1702 (s), 1746 (vs), 1789 (m), 2980 (m), 3355 (br, w) cm^{-1}; MS (ESI): *m/z* = 1542, 793 [*M* + Na]$^+$, 693, 627, 571, 471, 415; HRMS (ESI): *m/z* calcd. for $C_{35}H_{58}N_6O_{13}Na^+$: 793.3954 [*M* + Na]$^+$, found 793.3975.

4-((1′-((*S*)-1′′-(Methyloxy)-2′′-((*tert*-butoxycarbonyl)amino)-1′′-oxobutyl)-1*H*-1′,2′,3′-triazol-4′-yl)methyl)-(2*S*)-2-(*tert*-butoxycarbonylamino)-amidobutyl-methyl Ester (37a): From the azide **21** (452 mg, 1.26 mmol) and alkyne **31a** (357 mg, 1.26 mmol) in water (7.00 mL) and CH$_2$Cl$_2$ (7.00 mL), CuSO$_4$•5H$_2$O (6.44 mg, 25.8 µmol) and sodium ascorbate (57.0 mg, 0.29 mmol), 18 h, CuSO$_4$ 5 H$_2$O (5.90 mg, 23.6 µmol) and sodium ascorbate (49 mg, 0.25 mmol), 5 h, CuSO$_4$•5H$_2$O (6.08 mg, 24.4 µmol) and sodium ascorbate (42.0 mg, 0.21 mmol), 16 h, **37a** (447 mg, 0.70 mmol, 56 %) as a colorless oil. R_f = 0.08 (hexanes/EtOAc, 1:1); $[\alpha]_D^{20}$ = +5.79 (*c* = 1.07 in CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.43 [s, 9H; C(CH_3)$_3$] (alkyne), 1.49 [s, 18H; 2 × C(CH_3)$_3$], 2.36–2.54 (m, 1H; 3′′-H$_a$), 2.68 (dd, *J* = 17.1, 5.6 Hz, 1H; 3′-H$_a$), 2.73–2.87 (m, 1H; 3′′-H$_b$), 3.04 (dd, *J* = 17.1, 3.9 Hz, 1H; 3′-H$_b$), 3.68 (s, 3H; OMe), 3.72 (s, 3H; OMe), 4.27–4.73 (m, 5H; 4′′-H, 6-H, 2-H), 4.89 (m, 1H; 2′′-H), 5.52–5.72 (m, 1H; N*H*Boc), 6.93–7.11 (m, 1H; CON*H*), 7.55 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 28.1, 28.4 [3 × C(CH$_3$)$_3$], 31.2 (C-3′′), 35.4 (C-6), 36.0 (C-3′), 47.7 (C-4′′), 50.9 (C-2′), 52.2 (OMe), 52.6 (OMe), 55.7 (C-2′′), 84.0 [3 × *C*(CH$_3$)$_3$], 122.4 (C-5), 144.7 (C-4), 152.1 (3 × *C*OO*t*Bu), 170.5, 170.9, 172.7 ppm (C-1′, C-4′, C-1′′). FT-IR (ATR): $\tilde{\nu}$ = 463 (w), 647 (m), 728 (vs), 781 (m), 852 (m), 912 (m), 1049 (m), 1131 (vs), 1233 (s), 1366 (vs), 1438 (m), 1457 (m), 1518 (m), 1699 (s), 1737 (s), 1789 (w), 2255 (w), 2980 (w), 3331 (br, w) cm^{-1}; MS (ESI): *m/z* = 665 [*M* + Na]$^+$, 643, 599, 565, 543, 509, 487, 443, 431, 409, 387, 343, 313; HRMS (ESI): *m/z* calcd. for $C_{28}H_{46}N_6O_{11}Na^+$: 665.3117 [*M* + Na]$^+$, found 665.3059.

4-((1-((*S*)-5-(Methyloxy)-4-((*tert*-butoxycarbonyl)amino)-5-oxopentyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(bis(*tert*-butoxycarbonylamino))-amidobutyl-methyl Ester (37b): From the azide **22** (112 mg, 0.30 mmol) and alkyne **31a** (114 mg, 0.40 mmol) in water (1.90 mL) and CH$_2$Cl$_2$ (1.90 mL), CuSO$_4$•5H$_2$O (1.23 mg, 4.93 µmol) and sodium ascorbate (9.23 mg, 46.6 µmol), 19 h, CuSO$_4$•5H$_2$O (1.80 mg, 7.21 µmol) and sodium ascorbate (10.8 mg, 54.6 µmol), 6 h, CuSO$_4$•5H$_2$O (9.00 mg, 3.60 µmol) and sodium ascorbate (9.56 mg, 48.2 µmol), 18 h, **37b** (129 mg, 0.20 mmol, 67 %) as a colorless oil. R_f = 0.14 (hexanes/EtOAc, 1:2); $[\alpha]_D^{20}$ = –11.6 (*c* = 1.00 in CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.44 [s, 9H; C(CH_3)$_3$], 1.49 [s, 18H; 2 × C(CH_3)$_3$], 1.86–2.03 (m, 3H; 4′′-H, 3′′-H$_a$), 2.07–2.18 (m, 1H; 3′′-H$_b$), 2.68 (dd, *J* = 17.0, 5.7 Hz, 1H; 3′-H$_a$), 3.05 (dd, *J* = 17.0, 4.2 Hz, 1H; 3′-H$_b$), 3.69 (s, 3H; OMe), 3.71 (s, 3H; OMe), 4.36 (t, *J* = 6.9 Hz, 2H; 5′′-H), 4.45–4.61 (m, 3H; 6-H, 2′-H), 4.86–4.93 (m, 1H; 2′′-H), 5.50–5.76 (m, 1H; N*H*Boc), 6.91–7.12 (m, 1H; N*H*), 7.53 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.9, 27.0 (C-3′′, C-4′′), 28.1, 28.4 [3 × C(*C*H$_3$)$_3$], 34.5 (C-6), 36.1 (C-3′), 50.8 (C-5′′), 50.9 (C-2′) 52.2, 52.5 (2 × OMe), 57.2 (C-2′′), 83.8 [4 × *C*(CH$_3$)$_3$], 123.6 (C-5), 143.8 (C-4), 152.3 [3 × *C*OO*t*Bu], 170.8, 171.4, 172.3 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 462 (w), 647 (w), 732 (m), 784 (m), 853 (m), 917 (w), 1027 (m), 1051 (m), 1165 (vs), 1249 (s), 1304 (m), 1367 (vs), 1438 (m), 1456 (m), 1521 (m), 1701 (s), 1739 (s), 1789 (m), 2934 (m), 2979 (m), 3349 (w) cm^{-1}; MS (ESI): *m/z* = 695, 679 [*M* + Na]$^+$, 657, 613, 579, 557, 501, 445, 401, 357; HRMS (ESI): *m/z* calcd. for $C_{29}H_{48}N_6O_{11}Na^+$: 679.3273 [M + Na]$^+$, found 679.3272.

4-((1-((*S*)-4-(Methyloxy)-3-((Bis(*tert*-butoxycarbonyl)amino))-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(Bis(*tert*-butoxycarbonylamino))-amidobutyl-methyl Ester (37c): From the azide **21** (609 mg, 1.70 mmol) and alkyne **31b** (646 mg, 1.68 mmol) in water (9.50 mL) and CH$_2$Cl$_2$ (9.50 mL), CuSO$_4$•5H$_2$O (4.93 mg, 19.7 µmol) and sodium ascorbate (34.0 mg, 0.17 mmol), 22 h, CuSO$_4$•5H$_2$O (5.48 mg, 21.9 µmol) and sodium ascorbate (35.0 mg, 0.18 mmol), 6 h, CuSO$_4$•5H$_2$O (5.35 mg, 21.4 µmol) and sodium ascorbate (32.0 mg, 0.16 mmol), 20 h, **37c** (560 mg, 0.75 mmol, 45 %) as a colorless oil. R_f = 0.02 (hexanes/EtOAc, 2:1); $[\alpha]_D^{20}$ = –24.1 (*c* = 1.07 in CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.45 [s, 36H; 4 × C(CH_3)$_3$], 2.38–2.51 (m, 1H; 3′′-H$_a$), 2.58 (dd, *J* = 15.1, 5.8 Hz, 1H; 3′-H$_a$), 2.73–2.86 (m, 1H; 3′′-H$_b$), 3.10 (dd, *J* = 15.1, 7.6 Hz, 1H; 3′-H$_b$), 3.70 (s, 3H; OMe), 3.72 (s, 3H; OMe), 4.31–4.66 (m, 4H; 4′′-H, 6-H), 4.89 (dd, *J* = 8.0, 5.8 Hz, 1H; 2′′-H), 5.50 (dd, *J* = 7.3, 5.8 Hz, 1H; 2′-H), 6.27 (t, *J* = 5.2 Hz, 1H; N*H*), 7.60 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 28.1 [4 × C(CH_3)$_3$], 31.2 (C-3′′), 35.3 (C-6), 38.1 (C-3′), 47.8 (C-4′′), 52.6 (2 × OMe), 55.4 (C-2′), 55.7 (C-2′′), 83.6, 83.9 [4 × *C*(CH$_3$)$_3$], 122.6 (C-5), 144.7 (C-4), 151.9, 152.1 (4 × *C*OO*t*Bu), 169.8, 170.4, 170.9 ppm (C-1′, C-4′ C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 464 (w), 647 (w), 666 (w), 732 (m), 780 (m), 815 (w), 852 (m), 916 (m), 1000 (m), 1049 (m), 1114 (vs), 1141 (vs), 1167 (s), 1230 (s), 1312 (s), 1367 (vs), 1437 (m), 1457 (m), 1536 (m), 1699 (s), 1743 (vs), 1789 (m), 2980 (m), 3370 (br,w) cm^{-1}; MS (ESI): *m/z* = 765 [*M* + Na]$^+$, 743, 699, 665, 599, 565, 543, 509, 465, 443, 409, 387, 365, 343; HRMS (ESI): *m/z* calcd. for $C_{33}H_{54}N_6O_{13}Na^+$: 765.3641 [M + Na]$^+$, found 765.3643.

4-((1-((*S*)-5-(Methyloxy)-4-((Bis(*tert*-butoxycarbonyl)amino))-5-oxopentyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(bis(*tert*-butoxycarbonylamino))-amidobutyl-methyl Ester (37d): From the azide **22** (271 mg, 0.70 mmol) and alkyne **31b** (267 mg, 0.72 mmol) in water (8.30 mL) and CH$_2$Cl$_2$ (8.30 mL), CuSO$_4$•5H$_2$O (3.00 mg,

Full Paper
doi.org/10.1002/ejoc.202000811

12.0 μmol) and sodium ascorbate (25.0 mg, 0.13 mmol), 28 h, $CuSO_4$•$5H_2O$ (3.60 mg, 14.4 μmol) and sodium ascorbate (25.0 mg, 0.13 mmol), 4 d, **37d** (276 mg, 0.36 mmol, 51 %) as a colorless oil. R_f = 0.15 (hexanes/EtOAc, 1:2); $[\alpha]_D^{20}$ = –38.3 (*c* = 1.07 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 [2 × s, 36H; 4 × C(CH_3)$_3$], 1.81–2.00 (m, 3H; 4′′-H, 3′′-H_a), 2.04–2.23 (m, 1H; 3′′-H_b), 2.58 (dd, *J* = 15.0, 5.9 Hz, 1H; 3′-H_a), 3.09 (dd, *J* = 15.0, 7.5 Hz, 1H; 3′-H_b), 3.69 (2 × s, 6H; 2 × OMe), 4.35 (t, *J* = 7.0 Hz, 2H; 5′′-H), 4.43–4.59 (m, 2H; 6-H), 4.83–4.91 (m, 1 H, 2′-H), 6.41 (m, 1H; N*H*), 7.57 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1 (C-3′′, C-4′′), 28.1 [4 × C(CH_3)$_3$], 35.1 (C-6), 38.1 (C-3′), 50.1 (C-5′′), 52.4, 52.6 (2 × OMe), 55.4 (C-2′), 57.4 (C-2′′), 83.6 [4 × *C*(CH_3)$_3$], 122.6 (C-5), 144.7 (C-4), 151.9, 152.3 [2 × *C*OO*t*Bu], 169.8, 170.9 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 431 (w), 468 (w), 491 (w), 783 (m), 853 8m), 1003 (m), 1143 (vs), 1168 (s), 130 (s), 1251 (s), 1312 (s), 1368 (vs), 1457 (m), 1534 (m), 1701 (s), 1748 (vs), 1789 (m), 1961 (w), 2007 (w), 2153 (w), 2980 (m), 3379 (br, w) cm^{-1}; MS (ESI): *m/z* = 779 [*M* + Na]$^+$, 757, 713, 679, 613, 579, 557, 557, 501, 457, 401, 357; HRMS (ESI): *m/z* calcd. for $C_{34}H_{56}N_6O_{13}Na^+$: 779.3798 [*M* + Na]$^+$, found 779.3768.

3-((1′-((*S*)-3-(Methyloxy)-2-((*tert*-butoxycarbonyl)amino)-3-oxobutyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(*tert*-butoxycarbonylamino)-oxopropyl-methyl Ester (38a): From the azide **25** (515 mg, 2.11 mmol) and alkyne **35** (557 mg, 2.16 mmol) in water (22.0 mL) and CH_2Cl_2 (22.0 mL), $CuSO_4$•$5H_2O$ (5.8 mg, 23.2 μmol) and sodium ascorbate (42.0 mg, 0.21 mmol), 20 h, $CuSO_4$•$5H_2O$ (5.54 mg, 21.6 μmol) and sodium ascorbate (44 mg, 0.22 mmol), 5 h, Cu-SO_4•$5H_2O$ (5.23 mg, 20.8 μmol) and sodium ascorbate (40.0 mg, 0.20 mmol), 21 h, **38a** (660 mg, 1.32 mmol, 63 %) as a white solid. R_f = 0.04 (hexanes/EtOAc, 2:1). M.p. 82 °C; $[\alpha]_D^{20}$ = +29.6 (*c* = 1.13 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 [s, 9H; 2 × C(CH_3)$_3$], 3.71–376 (m, 4H; 3′-H_a, 1-OMe), 3.79 (s, 3H; 1′′-OMe), 3.92 (dd, *J* = 9.4, 3.3 Hz, 1H; 3′-H_b), 4.39–4.47 (m, 1H; 2′-H), 4.56–4.88 (m, 5H; 2′′-H, 3′′-H, 6-H), 5.26–5.59 (m, 2H; 2 × N*H*Boc), 7.47 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [2 × C(CH_3)$_3$], 52.6 (2 × OMe), 53.9 (C-2′), 51.1, 53.3, 54.1, 64.8 (C-2′′, C-3′′, C-6), 70.5 (C-3′), 80.2, 80.9 [2 × *C*(CH_3)$_3$], 123.9 (C-5), 144.7 (C-4), 155.3, 155.6 (2 × *C*OO*t*Bu), 169.6, 171.2 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 462 (w), 646 (w), 733 (m), 780 (w), 856 (w), 917 (w), 1027 (m), 1050 (s), 1108 (m), 1162 (vs), 1215 (s), 1249 8s), 1298 8m), 1367 (s), 1392 (m), 1438 (m), 1455 (m), 1506 (s), 1708 (vs), 1745 (s), 2977 (m), 3353 (br, w) cm^{-1}; MS (ESI): *m/z* = 540, 524 [*M* + Na]$^+$, 502, 468, 424, 402, 368, 346, 324; HRMS (ESI): *m/z* calcd. for $C_{21}H_{35}N_5O_9Na^+$: 524.2327 [M + Na]$^+$, found 524.2315. The spectroscopic data are in accordance with the literature.[33]

3-((1-((*S*)-4-(Methyloxy)-3-((Bis(*tert*-butoxycarbonyl)amino))-4-oxobutyl)-1*H*-1,2,3-tri-azol-4-yl)methyl)-(2*S*)-2-(*tert*-butoxycarbonylamino)-oxopropyl-methyl Ester (38b): From the azide **21** (381 mg, 1.06 mmol) and alkyne **35** (264 mg, 1.03 mmol) in water (11.0 mL) and CH_2Cl_2 (11.0 mL), $CuSO_4$•$5H_2O$ (5.50 mg, 22.0 μmol) and sodium ascorbate (40.0 mg, 0.20 mmol), 1 d, $CuSO_4$•$5H_2O$ (5.00 mg, 20.0 μmol) and sodium ascorbate (40 mg, 0.20 mmol), 3 d, $CuSO_4$•$5H_2O$ (2.90 mg, 11.6 μmol) and sodium ascorbate (20.0 mg, 0.10 mmol), 1 d, **38b** (368 mg, 0.60 mmol, 58 %) as a colorless oil. R_f = 0.06 (hexanes/EtOAc, 2:1); $[\alpha]_D^{20}$ = +1.68 (*c* = 1.07 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 [s, 9H; C(CH_3)$_3$ (alkyne)], 1.50 [s, 18H; C(CH_3)$_3$ (azide)], 2.38–2.54 (m, 1H; 3′′-H_a), 2.74–2.89 (m, 1H; 3′′-H_b), 3.70–3.78 (m, 7H; 2 × OMe, 3′-H_a), 3.89–3.96 (m, 1H; 3′-H_b), 4.34–4.56 (m, 3H; 2′-H, 4′′-H), 4.60–4.70 (m, 2H; 6-H), 4.85–4.95 (m, 1H; 2′′-H), 5.28–5.46 (m, 1H; *N*H), 7.57 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [2 × C(CH_3)$_3$] (azide), 28.5 (C(CH_3)$_3$) (alkyne), 31.2 (C-3′′), 47.8 (C-4′′), 52.6 (2 × OMe), 54.1 (C-2′), 55.7 (C-2′′), 65.0 (C-6), 70.6 (C-3′), 84.0 [3 × *C*(CH_3)$_3$], 123.0 (C-5), 144.7 (C-4), 152.2 (3 × *C*OO*t*Bu), 170.5, 171.2 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 416 (w), 463 (w), 575 (w), 647 (w), 733 (m), 781 (m), 810 (w), 853 (m), 913 (w), 1047 (s), 1112 (vs), 1131 (vs), 1163 (vs), 1231 (s), 1366 (vs), 1438 (m), 1457 (m), 1502 (m), 1704 (vs), 1744 (vs), 1791 (w), 2979 (m), 3369 (br, w) cm^{-1}; MS (ESI): *m/z* = 654, 638 [*M* + Na]$^+$, 616, 572, 554, 538, 516, 482, 464, 438, 416, 382, 360, 338, 316; HRMS (ESI): *m/z* calcd. for $C_{27}H_{45}N_5O_{11}Na^+$: 638.3008 [*M* + Na]$^+$, found 638.3031.

3-((1-((*S*)-5-(Methyloxy)-4-((Bis(*tert*-butoxycarbonyl)amino))-5-oxopentyl)-1*H*-1,2,3-triazol-4-yl)methyl)-(2*S*)-2-(*tert*-butoxycarbonylamino)-oxopropyl-methyl Ester (38c): From the azide **22** (121 mg, 0.32 mmol) and alkyne **35** (92.0 mg, 0.36 mmol) in water (1.90 mL) and CH_2Cl_2 (1.90 mL), $CuSO_4$•$5H_2O$ (0.8 mg, 3.2 μmol) and sodium ascorbate (6.66 mg, 33.6 μmol), 1 d, $CuSO_4$•$5H_2O$ (1.00 mg, 4.00 μmol) and sodium ascorbate (7.21 mg, 40.4 mmol), 1 d, Cu-SO_4•$5H_2O$ (8.30 mg, 33.2 μmol) and sodium ascorbate (7.54 mg, 38.1 mmol), 1 d, **38c** (183 mg, 0.29 mmol, 91 %) as a colorless oil. R_f = 0.21 (hexanes/EtOAc, 1:1); $[\alpha]_D^{20}$ = –16.21 (*c* = 0.73 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 [s, 9H; C(CH_3)$_3$], 1.46 [s, 18H; C(CH_3)$_3$], 1.82–2.23 (m, 4H; 3-H′′, 4-H′′), 3.68 (s, 3H; 1′′-OMe), 3.71 (s, 3H; 1-OMe), 3.72–3.74 (m, 1H; 3-H_α), 3.85–3.94 (m, 1H; 3-H_β), 4.33–4.39 (t, *J* = 6.9 Hz, 2H; 5′′-H), 4.39–4.45 (m, 1H; 2-H), 4.55–4.56 (m, 2H; 6′-H), 4.86 (dd, *J* = 8.9 Hz, 5.3 Hz, 1H; 2′′-H), 5.29–5.42 (m, 1H; N*H*), 7.48 ppm (s, 1H; 5′-H); ^{13}C NMR (100 MH z, $CDCl_3$): δ = 27.0, 27.1 (C-3′′, C-4′′), 28.0 (2 × C(CH_3)$_3$), 28.3 (C(CH_3)$_3$), 49.8 (C-5′′), 52.3 (1′′-OMe), 52.5 (1-OMe), 53.9 (C-2), 57.2 (C-2′′), 64.9 (C-6′), 70.3 (C-3), 80.0 (*C*(CH_3)$_3$), 83.5 [2 × *C*(CH_3)$_3$], 122.5 (C-5′), 144.4 (C-4′), 152.1 (2 × *C*OO*t*Bu), 155.5 (*C*OO*t*Bu), 170.8, 171.0 ppm (C-1, C′′-1); FT-IR (ATR): $\tilde{\nu}$ = 3374 (w, br), 2979 (m, br), 1790 (w), 1744 (s), 1703 (s), 1502 (m, br), 1456 (m), 1438 (m), 1366 (s), 1305 (m), 1249 (s, br), 1163 (vs), 1131 (vs), 1114 (vs), 1048 (m), 915 (w), 853 (m), 783 (m), 733 (m), 648 (w, br), 465 (w, br) cm^{-1}; MS (ESI): *m/z* = 652 [*M* + Na]$^+$, 552 [*M*-Boc + Na]$^+$, 496 [*M*-Boc-*tert*-butyl + Na]$^+$, 452 [*M*-2 × Boc + Na]$^+$, 396 [*M*-2 × Boc-*tert*-butyl + Na]$^+$; HRMS (ESI): *m/z* calcd. for $C_{28}H_{47}N_5O_{11}Na^+$: 652.3164 [*M* + Na]$^+$, found 652.3159.

3-(1-((*S*)-4-(Methyloxy)-3-((Bis(*tert*-butoxycarbonyl)amino))-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)-(2*S*)-2-(Bis(*tert*-butoxycarbonyl-amino))propyl-methyl Ester (39a): From the azide **21** (86.0 mg, 0.24 mmol) and alkyne **28** (79.0 mg, 0.24 mmol) in water (1.40 mL) and CH_2Cl_2 (1.40 mL), $CuSO_4$•$5H_2O$ (1.17 mg, 4.69 μmol) and sodium ascorbate (7.66 mg, 38.7 μmol), 1 d, $CuSO_4$•$5H_2O$ (1.17 mg, 4.69 μmol) and sodium ascorbate (11.0 mg, 55.5 μmol), 30 h, $CuSO_4$•$5H_2O$ (2.73 mg, 10.9 μmol) and sodium ascorbate (12.0 mg, 60.6 μmol), 19 h, **39a** (47.0 mg, 0.07 mmol, 29 %) as a colorless oil. R_f = 0.27 (hexanes/EtOAc, 2:1); $[\alpha]_D^{20}$ = –3.50 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42, 1.47 [2 × s, 36H; 4 × C(CH_3)$_3$], 2.33–2.48 (m, 1H; 3′′-H_a), 2.66–2.82 (m, 1H; 3′′-H_b), 3.23–3.34 (m, 1H; 3′-H_a), 3.50–3.61 (m, 1H; 3′-H_b), 3.70 (s, 3H, OMe), 3.72 (s, 3H, OMe), 4.30–4.50 (m, 2H; 4′′-H), 4.82–4.92 (m, 1H; 2′′-H), 5.16–5.23 (m, 1H; 2′-H), 7.39 ppm (d, *J* = 2.7 Hz, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0 (C-3′), 28.0, 28.1 [4 × C(CH_3)$_3$], 31.3 (C-3′′), 47.5 (C-4′′), 52.4 (OMe), 52.5 (OMe), 55.7 (C-2′′), 58.1 (C-2′), 83.4, 83.8 [4 × *C*(CH_3)$_3$], 122.4 (C-5), 144.0 (C-4), 151.7, 152.1 (4 × *C*OO*t*Bu), 170.4, 170.7 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 440 (w), 464 (w), 577 (w), 647 (w), 666 (w), 730 (s), 779 (m), 812 (w), 851 (m), 913 (m), 956 (w), 996 (m), 1011 (m), 1047 (m), 1087 (s), 1110 (vs), 1133 (vs), 1166 (s), 1226 (s), 1251 s), 1314 (m), 1366 (vs), 1437 (m), 1457 (m), 1554 (w), 1698 (s), 1742 (s), 1791 (m), 2980 (m) cm^{-1}; MS (ESI): *m/z* = 7.24, 708, 686 [*M* + Na]$^+$, 642, 608, 586, 542, 508, 486, 468, 452, 430, 408, 386, 374, 352, 330, 308, 286; HRMS (ESI): *m/z* calcd. for $C_{31}H_{51}O_{12}N_5Na^+$: 686.3607 [M + Na]$^+$, found 686.3604.

3-(1-((*S*)-5-(Methyloxy)-4-((Bis(*tert*-butoxycarbonyl)amino))-5-oxopentyl)-1*H*-1,2,3-triazol-4-yl)-(2*S*)-2-(Bis(*tert*-butoxycarbon-

ylamino))propyl-methyl Ester (39b): From the azide **22** (89.0 mg, 0.27 mmol) and alkyne **28** (107 mg, 0.29 mmol) in water (2.85 mL) and CH_2Cl_2 (2.85 mL), $CuSO_4$•$5H_2O$ (2.00 mg, 8.00 µmol) and sodium ascorbate (16.6 mg, 83.8 µmol), 28 h, $CuSO_4$•$5H_2O$ (2.60 mg, 10.4 µmol) and sodium ascorbate (19.6 mg, 98.9 mmol), 4 d, **39b** (149 mg, 0.21 mmol, 78 %) as a colorless oil. R_f = 0.63 (hexanes/EtOAc, 1:1); $[\alpha]_D^{20}$ = –20.9 (*c* = 1.00 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 [s, 18H; 2 × C(CH_3)$_3$], 1.47 [s, 18H; 2 × C(CH_3)$_3$], 1.83–2.01 (m, 3H; 4′′-H, 3′′-H_a), 2.07–2.23 (m, 1H; 3′′-H_b), 3.28 (dd, *J* = 15.2, 9.8 Hz, 1H; 3′-H_a), 3.57 (dd, *J* = 15.2, 9.8 Hz, 1H; 3′-H_b), 3.70 (s, 3H; OMe), 3.73 (s, 3H; OMe), 4.23–4.39 (m, 2H; 5′′-H), 4.83–4.92 (m, 1H; 2′′-H), 5.19–5.25 (m, 1H; 2′-H), 7.35 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 28.1 (4 × [C(CH_3)$_3$]), 49.8 (C-5′′), 52.4 (OMe), 57.4 (C-2′′), 58.1 (C-2′), 83.4, 83.6 [4 × [*C*(CH_3)$_3$], 122.4 (C-5), 143.9 (C-4), 151.7, 152.3 (4 × *C*OO*t*Bu), 170.7, 170.9 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 416 (w), 442 (w), 464 (w), 493 (w), 583 (w), 647 (w), 666 (w), 731 (s), 780 (m), 851 (m), 913 (m), 957 (w), 998 (m), 1048 8m), 1088 (s), 1133 (vs), 1167 (s), 1225 (s), 1250 (s), 1313 (m), 1366 (s), 1437 (w), 1457 (w), 1478 (w), 1555 (w), 1698 (s), 1743 (s), 1790 (w), 2937 (w), 2980 (m), 3140 (w) cm^{-1}; MS (ESI): *m/z* = 722 [*M* + Na]$^+$, 700, 656, 622, 600, 556, 522, 500, 466, 422, 400, 388, 366, 344, 322, 300; HRMS (ESI): *m/z* calcd. for $C_{32}H_{53}N_5O_{12}Na^+$: 722.3583 [*M* + Na]$^+$, found 722.3583.

General Procedure for the Deprotection of Triazoles to Acids 36–39·2HCl: Analogous to ref.[35] a 1 M solution of NaOH (2.54 mL, 2.54 mmol) was added to a solution of the respective triazole **36**–**39** (1.00 mmol) in MeOH (55 mL), and the reaction mixture stirred at r.t. for several days. After concentration of the reaction mixture, the residue was taken up in H_2O (18.2 mL) and a 6 M solution of HCl (8.00 mL) was added. The reaction mixture was stirred for several days and subsequently concentrated under reduced pressure. In the presence of the base, racemization is possible but it was not checked.

(1*S*)-1-Carboxy-3-{4-[(L-γ-glutamylamino)methyl]-1*H*-1,2,3-triazol-1-yl}propan-1-aminium Dichloride (36a·2HCl): From **36a** (16.0 mg, 21.1 µmol) in MeOH (1.20 mL), 1 M NaOH (0.06 mL, 0.06 mmol), 2 d; H_2O (0.40 mL), 6 M HCl (0.18 mL, 11.0 mmol), 3 d, **36a·2HCl** (17.0 mg, quant.), white solid. $[\alpha]_D^{20}$ = +0.72 (*c* = 1.53 in H_2O); ^1H NMR (500 MHz, $CDCl_3$): δ = 2.06–2.16 (m, 1H; 3′-H_a), 2.18–224 (m, 1H; 3′-H_b), 2.40–2.47 (m, 2H; 4′-H), 2.55–2.61 (m, 2H; 3′′-H), 4.02–4.05 (m, 1H; 2′′-H), 4.39–4.43 (m, 1H; 2′-H), 4.70–4.74 (m, 2H; 4′′-H), 4.81–4.83 (m, 2H; 6-H), 8.09 ppm (s, 1H; 5-H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 25.6 (C-3′), 28.6 (C-4′), 30.0 (C-3′′), 33.1 (C-6), 46.5 (C-4′′), 50.0 (C-2′′), 56.4 (C-2′), 125.4 (C-5), 158.4 (C-5′), 175.9, 176.8 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 535 (w), 598 (w), 787 (w), 1056 (m), 1159 (s), 1212 (s), 1349 (m), 1418 (s), 1447 (s), 1510 (m), 1708 (vs), 1975 (w), 2928 (s) cm^{-1}; MS (ESI): *m/z* = 397, 375, 367, 353 [*M* + Na]$^-$, 335, 327, 252, 224, 176, 146, 128; HRMS (ESI): *m/z* calcd. for $C_{12}H_{22}N_6O_5Na^-$: 353.1544 [*M* + Na]$^-$, found 353.1525.

(1*S*)-1-Carboxy-4-{4-[(L-γ-glutamylamino)methyl]-1*H*-1,2,3-triazol-1-yl}butan-1-aminium Dichloride (36b·2HCl): From **36b** (18.0 mg, 23.3 µmol) in MeOH (1.40 mL), 1 M NaOH (0.07 mL, 0.07 mmol), 3 d; H_2O (0.50 mL), 6 M HCl (0.19 mL, 11.6 mmol), 2 d, **36b·2HCl** (21.0 mg, quant.), white solid. $[\alpha]_D^{20}$ = +0.98 (*c* = 0.93 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.81–2.31 (m, 6H; 3′-H, 3′′-H, 4′′-H), 2.45–2.56 (t, *J* = 7.2 Hz, 2H; 4′-H), 4.09–4.15 (m, 1H; 2′′-H), 4.24–4.34 (m, 1H; 2′-H), 4.51 (s, 2H; 6-H), 4.54–4.60 (m, 2H; 5′′-H), 8.23 ppm (s, 1H; 5-H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 25.0, 25.6, 26.5 (C-3′, C-3′′, C-4′′), 30.2 (C-4′), 32.9 (C-6), 49.8 (C-5′′), 52.2 (C-2′′), 56.4 (C-2′), 124.9 (C-5), 141.9 (C-4), 158.0 (C-5′), 171.4, 176.9 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 413(w), 460 (w), 527 (w), 596 (w), 784 (w), 827 (w), 1030 (w), 1053 (w), 1155 (s), 1208 (s), 1345 (m), 1415 (m), 1446 (m), 1500 (m), 1708 (vs), 2921 (m) cm^{-1}; MS (ESI): *m/z* = 391, 381, 365 [*M* + Na]$^+$, 343 [*M* + H]$^+$, 325, 310, 294, 279, 252, 236, 223, 214, 181, 165, 152, 140, 122; HRMS (ESI): *m/z* calcd. for $C_{13}H_{22}N_6O_5Na^+$: 365.1544 [*M* + Na]$^+$, found 365.1535. Impurities could not be removed because of the purification problems due to the charged species.

(1*S*)-3-{4-[(L-β-Aspartylamino)methyl]-1*H*-1,2,3-triazol-1-yl}-1-carboxypropan-1-aminium Dichloride (37a·2HCl/37c·2HCl): From **37a (**47.0 mg, 63.3 µmol) in MeOH (3.60 mL), 1 M NaOH (0.16 mL, 0.16 mmol), 6 d; H_2O (1.20 mL), 6 M HCl (0.53 mL, 32.4 mmol), 5 d, **37a·2HCl** (44.0 mg, quant.), yellow solid. From **37c (**43.0 mg, 66.9 µmol) in MeOH (3.80 mL), 1 M NaOH (0.19 mL, 0.19 mmol), 6 d; H_2O (1.25 mL), 6 M HCl (0.55 mL, 33.6 mmol), 5 d, **37c·2HCl** (48.0 mg, quant.), yellow solid. $[\alpha]_D^{20}$ = +0.75 (*c* = 1.00 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50–2.77 (m, 2H; 3′′-H), 3.10 (t, *J* = 5.4 Hz, 2H; 3′-H), 4.12 (t, *J* = 6.6 Hz, 1H; 2′′-H), 4.44 (t, *J* = 5.4 Hz, 1H; 2′-H), 4.54 (s, 2H; 6-H), 4.71–4.76 (m, 2H; 4′′-H), 8.08 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (C-3′′), 34.2 (C-6), 34.4 (C-3′), 46.7 (C-4′′), 49.5 (C-2′), 50.1 (C-2′′), 124.7 (C-5), 144.1 (C-4), 170.7, 170.8, 170.9 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 412 (w), 471 (w), 517 (w), 579 (w), 621 (w), 786 (w), 848 (w), 1017 (m), 1056 (m), 1089 (m), 1155 (s), 1226 (vs), 1373 (m), 1437 (s), 1554 (m), 1662 (s), 1717 (vs), 1741 (vs), 2929 (s) cm^{-1}; MS (ESI): *m/z* = 433, 399, 377, 353, 337, 315 [*M* – H]$^+$, 297, 269, 200, 177, 155; HRMS (ESI): *m/z* calcd. for $C_{11}H_{19}N_6O_5^+$: 315.1411 [*M* – H]$^+$, found 315.1406. Impurities could not be removed because of the purification problems due to the charge species.

(1*S*)-3-{4-[(L-β-Aspartylamino)methyl]-1*H*-1,2,3-triazol-1-yl}-1-carboxybutan-1-aminium Dichloride (37b·2HCl): From **37b (**62.0 mg, 94.5 µmol) in MeOH (5.00 mL), 1 M NaOH (0.24 mL, 0.24 mmol), 2 d; H_2O (1.65 mL), 6 M HCl (0.72 mL, 44.0 mmol), 3 d, **37b·2HCl** (70.0 mg, quant.), white solid. $[\alpha]_D^{20}$ = +1.87 (*c* = 0.87 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.84–2.25 (m, 2H; 3′′-H, 4′′-H), 3.08 (t, *J* = 5.3 Hz, 2H; 3′-H), 4.14 (t, *J* = 6.1 Hz, 1H; 2′′-H), 4.43 (t, *J* = 5.3 Hz, 1H; 2′-H), 4.49–4.63 (m, 4H; 5′′-H, 6-H), 8.18 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (C-4′′), 26.6 (C-3′′), 33.7 (C-6), 34.3 (C-3′), 49.5 (C-2′), 50.8 (C-5′′), 52.2 (C-2′′), 125.5 (C-5), 142.8 (C-4), 170.9, 171.4, 172.4 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 419 (w), 439 (w), 483 (w), 542 (w), 698 (m), 734 (m), 1118 (m), 1168 (m), 1260 (m), 1377 (m), 1461 (m), 1714 (s), 1969 (w), 1995 (w), 2014 (w), 2062 (w), 2110 (w), 2151 (w), 2181 (w), 2210 (w), 2853 (s), 2924 (vs) cm^{-1}; MS (ESI): *m/z* = 389, 371, 367, 353 [*M* + Na]$^-$, 349, 327, 309, 292; HRMS (ESI): *m/z* calcd. for $C_{12}H_{22}N_6O_5Na^-$: 353.1544 [*M* + Na]$^-$, found 353.1544.

(*S*)-2-{4-[((S)-2-Ammonio-2-carboxyethoxy]methyl)-1*H*-1,2,3-triazol-4-yl}-1-carboxyethan-1-aminium Dichloride (38a·2HCl): From **38a** (43.0 mg, 85.7 µmol) in MeOH (4.80 mL), 1 M NaOH (0.22 mL, 0.22 mmol), 6 d; H_2O (1.65 mL), 6 M HCl (0.70 mL, 42.7 mmol), 5 d, **38a·2HCl** (54.0 mg, quant.), yellow solid. $[\alpha]_D^{20}$ = +0.71 (*c* = 1.00 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.95–4.10 (m, 2H; 3′-H), 4.36 (t, *J* = 3.7 Hz, 1H; 2′-H), 4.75–4.77 (m, 3H; 2′′-H, 6-H), 5.10–5.16 (m, 2H; 3′′-H), 8.17 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.9 (C-3′′), 52.6 (C-2′′), 53.1 (C-2′), 63.3 (C-6), 66.8 (C-3′), 126.4 (C-5), 143.8 (C-4), 168.7, 169.7 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 422 (w), 506 (w), 614 (w), 842 (w), 906 (w), 1074 (m), 1156 (m), 1215 (s), 1414 (m), 1505 (m), 1591 (m), 1736 (vs), 2833 (s) cm^{-1}; MS (ESI): *m/z* = 651, 607, 548, 498, 471, 439, 398, 340, 318, 296, 274 [*M* – H]$^+$, 243, 231, 209, 187, 164, 141; HRMS (ESI): *m/z* calcd. for $C_9H_{16}N_5O_5^+$: 274.1146 [*M* – H]$^+$, found 274.1144.

(*S*)-3-{4-[((*S*)-2-Ammonio-2-carboxyethoxy]methyl)-1*H*-1,2,3-triazol-4-yl}-1-carboxypropan-1-aminium Dichloride (38b·2HCl): From **38b** (52.0 mg, 84.5 µmol) in MeOH (4.40 mL), 1 M NaOH

(0.20 mL, 0.20 mmol), 6 d; H_2O (1.50 mL), 6 M HCl (0.65 mL, 39.7 mmol), 3 d, **38b·2HCl** (57.0 mg, quant.), yellow solid. $[\alpha]_D^{20}$ = +0.6 (*c* = 1.00 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.47–2.69 (m, 2H; 3′′-H), 3.90–4.04 (m, 2H; 3′-H), 4.04–4.11 (m, 1H; 2′′-H), 4.30 (t, *J* = 3.6 Hz, 1H; 2′-H), 4.65–4.71 (m, 2H; 4′′-H), 4.73–4.76 (m, 2H; 6-H), 8.13 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (C-3′′), 46.7 (C-4′′), 50.2 (C-2′′), 53.1 (C-2′), 63.3 (C-6), 66.8 (C-3′), 125.9 (C-5), 143.3 (C-4), 169.8, 170.8 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 522 (m), 734 (w), 825 (w), 909 (w), 1056 (m), 1097 (m), 1155 (m), 1218 (m), 1344 (w), 1422 (m), 1498 (m), 1600 (m), 1734 (s), 1934 (w), 2924 (s), 3367 (m) cm^{-1}; MS (ESI): *m/z* = 458, 439, 413, 372, 350, 326, 310, 288 $[M - H]^+$, 257, 239, 201, 149, 131; HRMS (ESI): *m/z* calcd. for $C_{10}H_{18}N_5O_5^+$: 288.1302 $[M - H]^+$, found 288.1284.

(*S*)-4-{4-[((*S*)-2-Ammonio-2-carboxyethoxy]methyl)-1*H*-1,2,3-triazol-4-yl}-1-carboxybutan-1-aminium Dichloride (38c·2HCl): From **38c** (42.0 mg, 66.7 µmol) in MeOH (3.80 mL), 1 M NaOH (0.18 mL, 0.18 mmol), 3 d; H_2O (1.30 mL), 6 M HCl (0.55 mL, 33.6 mmol), 2 d, **38c·2HCl** (47.0 mg, quant.), white solid. $[\alpha]_D^{20}$ = +7.28 (*c* = 1.00 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.86–2.09 (m, 4H; 3′′-H, 4′′-H), 4.00–4.08 (m, 2H; 3′-H), 4.13–4.17 (m, 1H; 2′′-H), 4.37 (t, *J* = 3.7 Hz, 1H; 2′-H), 4.59 (t, *J* = 6.7 Hz, 2H; 5′′-H), 4.73–4.77 (m, 2H; 6-H), 8.18 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1 (C-4′′), 26.6 (C-3′′), 50.0 (C-5′′), 52.2 (C-2′′), 53.1 (C-2′), 63.1 (C-6), 66.8 (C-3′), 125.7 (C-5), 142.9 (C-4), 169.7, 171.5 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 530 (m), 614 (m), 781 (m), 829 (m), 1031 (s), 1053 (s), 1106 (cs), 1156 (vs), 1211 (vs), 1342 (m), 1411 (s), 1450 (m), 1501 (s), 1595 (s), 1734 (vs), 1970 (w), 2852 (vs) cm^{-1}; MS (ESI): *m/z* = 368, 346, 340, 324 $[M + Na]^+$, 302 $[M + H]^+$, 279, 259, 253, 237, 229, 215, 197, 187, 169, 158, 152, 141, 124, 116; HRMS (ESI): *m/z* calcd. for $C_{11}H_{19}N_5O_5Na^+$: 324.1278 $[M + Na]^+$, found 324.1270.

(1*S*)-3-{4-[(2*S*)-2-Ammonio-2-carboxyethyl]-1*H*-1,2,3-triazol-1-yl}-1-carboxypropan-1-aminium Dichloride (39a·2HCl): From **39a** (26.0 mg, 37.9 µmol), in MeOH (2.20 mL), 1 M NaOH (0.10 mL, 0.10 mmol), 3 d; H_2O (0.75 mL), 6 M HCl (0.31 mL, 18.9 mmol), 2 d, **39a·2HCl** (26.0 mg, quant.), white solid. $[\alpha]_D^{20}$ = +0.22 (*c* = 0.93 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.52–2.74 (m, 2H; 3′′-H), 3.49 (d, *J* = 6.0 Hz, 2H; 3′-H), 4.06–4.14 (m, 1H; 2′′-H), 4.48 (t, *J* = 6.0 Hz, 1H; 2′-H), 4.74 (t, *J* = 7.0 Hz, 2H; 4′′-H), 8.06 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6 (C-3′), 30.2 (C-3′′), 46.4 (C-4′′), 50.2 (C-2′′), 52.6 (C-2′), 125.4 (C-5), 141.0 (C-4), 170.9, 171.0 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 420 (w), 521 (w), 617 (w), 811 (m), 1057 (m), 1151 (m), 1208 (s), 120 (m), 1498 (m), 1593 (m), 1734 (vs), 2852 (m), 3373 (m) cm^{-1}; MS (ESI): *m/z* = 324, 318, 308, 302, 296, 280 $[M + Na]^+$, 270, 258 $[M + H]^+$, 253, 249, 237, 221, 212, 202, 197, 189, 181, 163, 149; HRMS (ESI): *m/z* calcd. for $C_9H_{15}N_5O_4Na^+$: 280.1016 $[M + Na]^+$, found 280.1018.

(1*S*)-4-{4-[(2*S*)-2-Ammonio-2-carboxyethyl]-1*H*-1,2,3-triazol-1-yl}-1-carboxybutan-1-aminium Dichloride (39b·2HCl): From **39b** (31.0 mg, 44.3 µmol) in MeOH (2.60 mL), 1 M NaOH (0.13 mL, 0.13 mmol), 3 d; H_2O (0.85 mL), 6 M HCl (0.37 mL, 22.6 mmol), 2 d, **39b·2HCl** (34.0 mg, quant.), white solid. $[\alpha]_D^{20}$ = +1.1 (*c* = 1.00 in H_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.83–2.24 (m, 4H; 3′′-H, 4′′-H), 3.48 (d, *J* = 6.0 Hz, 2H; 3′-H), 4.14 (t, *J* = 6.0 Hz, 1H; 2′′-H), 4.47 (t, *J* = 6.0 Hz, 1H; 2′-H), 4.54 (t, *J* = 6.5 Hz, 2H; 5′′-H), 8.04 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1 (C-4′′), 25.6 (C-3′), 26.7 (C-3′′), 49.6 (C-5′′), 52.3 (C-2′′), 52.5 (C-2′), 125.2 (C-5), 140.8 (C-4), 170.8, 171.5 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 427 (w), 518 (m), 615 (w), 670 (w), 836 (m), 1032 (m), 1056 (m), 1160 (m), 1207 (s), 1420 (m), 1498 (m), 1593 (m), 1733 (vs), 2554 (s), 2615 (s), 2852 (s), 3379 (m) cm^{-1}; MS (ESI): *m/z* = 338, 324, 316, 308, 300, 294 $[M + Na]^+$, 286, 280, 272 $[M + H]^+$, 258, 249, 237, 227, 216, 188, 171, 157, 130, 116; HRMS (ESI): *m/z* calcd. for $C_{10}H_{17}N_5O_4Na^+$: 294.1173 $[M + Na]^+$, found 294.1171.

General Procedure for the *N*-Alkylation of Triazoles 36–38: Analogous to ref.[36] MeI (32.0–33.0 mmol) was added to a solution of the respective triazole **36**–**38** (1.00 mmol) in MeCN (2.00 mL), and the reaction mixture was heated at 55 °C for 4–6 d. After removal of the solvent, the residue was purified by chromatography on HI treated SiO_2 with EtOAc, CH_2Cl_2, and CH_2Cl_2/MeOH (15:1).

1-((*S*)-3-(Bis(*tert*-butoxycarbonyl)amino)-4-methoxy-4-[((*S*)-4-(bis(*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanamido)methyl]-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (36a-MeI): From **36a** (130 mg, 0.17 mmol) in MeCN (7.60 mL), MeI (0.35 mL, 5.62 mmol), 5 d, yellow wax (149 mg, 0.17 mmol, quant.). $[\alpha]_D^{20}$ = –12.9 (*c* = 0.76 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 [s, 18H; 2 × $C(CH_3)_3$], 1.47 [s, 18H; 2 × $C(CH_3)_3$], 2.16–2.44 (m, 4H; 3′-H, 4′-H), 2.45–2.58 (m, 1H; 3′′-H_a), 2.80–3.05 (m, 1H; 3′′-H_b), 3.66 (s, 3H; OMe), 3.71 (s, 3H; OMe), 4.46 (s, 3H; CH_3), 4.56–4.72 (m, 4H; 6-H, 4′′-H), 4.78–4.97 (m, 2H; 2′′-H, 2′-H), 8.80 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (C-3′), 28.1 [4 × $C(CH_3)_3$], 30.1 (C-3′′), 31.9 (C-6), 32.1 (C-4′), 39.6 (CH_3), 51.7 (C-4′′), 52.2, 52.7 (2 × OMe), 55.1 (C-2′′), 58.1 (C-2′), 83.5, 84.3 [4 × $C(CH_3)_3$], 131.3 (C-5), 142.4 (C-4), 151.7, 152.0 [4 × *C*OO*t*Bu], 169.8, 170.8, 173.1 ppm (C-1′, C-5′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 443 (w), 463 (w), 573 (w), 644 (m), 665 (w), 728 (vs), 783 (m), 851 (m), 916 (m), 1014 (m), 1037 (m), 1092 (s), 1139 (vs), 1231 (s), 1366 (s), 1456 (m), 1525 (m), 1696 (m), 1740 (s), 1787 (m), 2196 (w), 2980 (m), 3235 (w) cm^{-1}; MS (ESI positive): *m/z* = 771 $[M]^+$, 671; HRMS (ESI positive): *m/z* calcd. for $C_{35}H_{59}N_6O_{13}^+$: 771.4135 $[M]^+$, found 771.4131; MS (ESI negative): *m/z* = 127 $[M]^-$; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9039.

4-[((*S*)-4-(Bis(*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanamido)methyl]-1-((*S*)-4-(bis(*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (36b-MeI): From **36b** (115 mg, 0.15 mmol) in MeCN (6.83 mL), MeI (0.30 mL, 4.82 mmol), 5 d, yellow solid (115 mg, 0.13 mmol, 86 %). M.p. 57 °C; $[\alpha]_D^{20}$ = –26.8 (*c* = 0.82 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 [s, 18H; 2 × $C(CH_3)_3$], 1.50 [s, 18H; 2 × $C(CH_3)_3$], 1.88–2.02 (m, 1H; 3′′-H_a), 2.08–2.51 (m, 7H; 3′′-H_b, 4′′-H, 4′-H, 3′-H), 3.69 (s, 3H; OMe), 3.72 (s, 3H; OMe), 4.47 (s, 3H; CH_3), 4.57–4.66 (m, 2H; 5′′-H), 4.67–4.73 (m, 2H; 6-H), 4.81–4.90 (m, 2H; 2′-H, 2′′-H), 8.85 ppm (s, 1H; 5-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.7 (C-3′), 26.1 (C-4′′), 26.9 (C-3′′), 28.2 [4 × $C(CH_3)_3$], 32.1 (C-4′, C-6), 52.3 (OMe), 52.6 (OMe), 53.8 (C-5′′), 57.1 (C-2′′), 58.2 (C-2′), 83.7, 83.9 [4 × $C(CH_3)_3$], 131.3 (C-5), 142.7 (C-4), 151.9, 152.3 (4 × *C*OO*t*Bu), 170.6, 170.9, 173.3 ppm (C-1′, C-5′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 461 (w), 665 (w), 733 (w), 784 (m), 853 (m), 909 (w), 1013 (w), 1119 (s), 1142 (vs), 1250 (s), 1313 (m), 1367 (vs), 1456 (m), 1529 (m), 1698 (s), 1743 (s), 1787 (m), 2979 (m), 3221 (w) cm^{-1}; MS (ESI positive): *m/z* = 786 $[M]^+$, 685; HRMS (ESI positive): *m/z* calcd. for $C_{36}H_{61}N_6O_{13}^+$: 785.4291 $[M + Na]^+$, found 785.4289; MS (ESI negative): *m/z* = 157, 127 $[M]^-$; HRMS (ESI negative): calcd. for I^-: 126.9039 $[M]^-$, found 126.9041.

1-((*S*)-3-(Bis(*tert*-butoxycarbonyl)amino))-4-methoxy-4-oxobutyl)-4-(((*S*)-3-((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanamido)methyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (37a-MeI): From **37a** (142 mg, 0.22 mmol) in MeCN (4.20 mL), MeI (0.44 mL, 7.07 mmol), 6 d, orange solid (180 mg, 0.22 mmol, quant.). M.p. 66 °C; $[\alpha]_D^{20}$ = +3.3 (*c* = 0.88 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9H; $C(CH_3)_3$), 1.49 [s, 18H; 2 × $C(CH_3)_3$], 2.46–2.54 (m, 1H; 3′′-H_a), 2.75–2.86 (m, 1H; 3′-H_a), 2.88–2.98 (m, 1H; 3′′-H_b), 3.00–3.09 (m, 1H; 3′-H_b), 3.72 (s, 3H; OMe), 3.75 (s, 3H; OMe), 4.40 (s, 3H; CH_3), 4.47–4.59 (m, 1H; 2′-H), 4.63–4.71 (m, 2H; 4′′-H), 4.77–4.84 (m, 2H; 6-H), 4.85–4.96 (m, 1H; 2′′-H), 5.63–5.82 (m, 2H; 2 × N*H*), 8.90 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 28.4, 28.5 [3 × C(CH_3)$_3$], 30.3 (C-3′′), 32.9 (C-6), 36.6 (C-3′), 39.3 (CH_3), 51.8 (C-2′), 52.2 (C-4′′), 52.8 (OMe), 55.1 (C-2′′), 80.8, 84.6 [3 × C(CH_3)$_3$], 131.2 (C-5), 142.5 (C-4), 152.1 (3 × COO*t*Bu), 169.9, 171.9, 172.3 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): ṽ = 645 (w), 733 (m), 783 (m), 855 (m), 917 (w), 1024 (m), 1053 (m), 1164 (vs), 1250 (s), 1367 (vs), 1392 (s), 1438 (m), 1513 (s), 1709 (vs), 1988 (w), 2040 (w), 2092 (w), 2184 (w), 2979 (m), 3341 (m) cm^{-1}; MS (ESI positive): *m/z* = 657 $[M]^+$, 625, 601, 557, 525, 501, 469, 451, 413, 401, 369, 342, 310, 286, 254; HRMS (ESI positive): *m/z* calcd. for $C_{29}H_{49}N_6O_{11}^+$: 657.3454 $[M]^+$, found 657.3459; MS (ESI negative): *m/z* = 255, 241, 227, 157, 127 $[M]^-$; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9061.

1-((*S*)-4-(Bis(*tert*-butoxycarbonyl)amino))-5-methoxy-5-oxopentyl)-4-(((*S*)-3-((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanamido)methyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (37b-MeI): From **37b** (146 mg, 0.22 mmol) in MeCN (4.20 mL), MeI (0.45 mL, 7.23 mmol), 5 d, yellow solid (158 mg, 0.20 mmol, 90 %). M.p. 64 °C; $[\alpha]_D^{20}$ = –6.4 (*c* = 1.01 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 [s, 9H; C(CH_3)$_3$], 1.49 [s, 18H; 2 × C(CH_3)$_3$], 1.89–1.98 (m, 1H; 3′′-H_a), 2.08–2.22 (m, 3H; 3′′-H_b, 4′′-H), 2.83 (dd, *J* = 16.7, 4.2 Hz, 1H; 3′-H_a), 3.06 (dd, *J* = 16.7, 5.5 Hz, 1H; 3′-H_b), 3.65 (s, 3H; OMe), 3.70 (s, 3H; OMe), 4.40 (s, 3H; CH_3), 4.47–4.56 (m, 1H; 2′-H), 4.60 (t, *J* = 7.1 Hz, 2H; 5′′-H), 4.77–4.83 (m, 2H; 6-H), 4.83–4.88 (m, 1H; 2′′-H), 5.73 (d, *J* = 8.3 Hz, 1H; N*H*Boc), 8.57–8.72 (m, 1H; CON*H*), 8.93 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (C-4′′), 26.8 (C-3′′), 28.1, 28.5 [3 × C(CH_3)$_3$], 33.0 (C-6), 36.6 (C-3′), 39.3 (CH_3), 51.1 (C-2′), 52.2 (OMe), 52.5 (OMe), 53.8 (C-5′′), 57.0 (C-2′′), 80.7, 83.9 [3 × C(CH_3)$_3$], 131.0 (C-5), 142.5 (C-4), 152.3 [3 × COO*t*Bu], 170.7, 171.9, 172.3 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): ṽ = 462 (w), 644 (w), 731 (s), 783 (m), 852 (m), 917 (m), 1024 (m), 1120 (s), 1142 (vs), 1162 (s), 1251 (s), 1312 (m), 1366 (s), 1437 (m), 1455 (m), 1509 (m), 1697 (s), 2979 (m), 3368 (w) cm^{-1}; MS (ESI positive): *m/z* = 671 $[M]^+$, 639, 615, 583, 571, 539, 515, 483, 465, 439, 415, 383, 310, 286, 254; HRMS (ESI positive): *m/z* calcd. for $C_{30}H_{51}N_6O_{11}^+$: 671.3610 $[M]^+$, found 671.3612; MS (ESI negative): *m/z* = 241, 227, 157, 127 $[M]^-$; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9038.

4-((*S*)-3-(Bis(*tert*-butoxycarbonyl)amino))-4-methoxy-4-oxobutanamido)methyl)-1-((*S*)-3-(bis(*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (37c-MeI): From **37c** (189 mg, 0.25 mmol) in MeCN (4.80 mL), MeI (0.51 mL, 8.19 mmol), 6 d, yellow solid (211 mg, 0.24 mmol, 96 %). M.p. 62 °C; $[\alpha]_D^{20}$ = –15.3 (*c* = 1.05 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [s, 18H; C(CH_3)$_3$], 1.49 [s, 18H; C(CH_3)$_3$], 2.41–2.57 (m, 1H; 3′′-H_a), 2.58–2.68 (m, 1H; 3′-H_a), 2.85–3.00 (m, 1H; 3′′-H_b), 3.17–3.30 (m, 1H; 3′-H_b), 3.68 (s, 3H; OMe), 3.73 (s, 3H; OMe), 4.42 (s, 3H; CH_3), 4.59–4.94 (m, 6H; 4′′-H, 2′′-H, 6-H), 5.48 (t, *J* = 6.7 Hz, 1H; 2′-H), 8.43–8.57 (m, 1H; N*H*), 8.81–8.84 ppm (m, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [4 × C(CH_3)$_3$], 30.3 (C-3′′), 32.5 (C-6), 37.4 (C-3′), 39.3 (CH_3), 51.8 (C-4′′), 52.5 (OMe), 52.8 (OMe), 55.1 (C-2′, C-2′′), 83.8, 84.5 [4 × [C(CH_3)$_3$], 130.9 (C-5), 142.8 (C-4), 151.5, 152.1 (4 × COO*t*Bu), 169.8 (C-4′), 170.8, 171.0 ppm (C-1′, C-1′′); FT-IR (ATR): ṽ = 446 (w), 664 (w), 734 (w), 782 (w), 850 (w), 915 (w), 1000 (w), 1119 (s), 1143 (vs), 1166 (s), 1234 (s), 1272 (s), 1315 (m), 1367 (vs), 1456 (m), 1532 (m), 1699 (s), 1744 (vs), 1787 (m), 2134 (w), 2980 (m), 3226 (w) cm^{-1}; MS (ESI positive): *m/z* = 757 $[M]^+$, 725, 657, 625, 601, 557, 525, 501, 483, 469, 451, 401, 369, 310, 286; HRMS (ESI positive): *m/z* calcd. for $C_{34}H_{57}N_6O_{13}N^+$: 757.3978 $[M]^+$, found 757.3981; MS (ESI negative): *m/z* = 265, 255, 241, 227, 157, 127 $[M]^-$; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9047.

4-((*S*)-3-(Bis(*tert*-butoxycarbonyl)amino))-4-methoxy-4-oxobutanamido)methyl)-1-((*S*)-4-(bis(*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (37d-MeI): From **37d** (110 mg, 0.15 mmol) in MeCN (3.20 mL), MeI (0.30 mL, 4.82 mmol), 5 d, yellow solid (124 mg, 0.14 mmol, 93 %). M.p. 59 °C; $[\alpha]_D^{20}$ = –33.1° (*c* = 0.99 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48, 1.49 [2 × s, 36H; 4 × C(CH_3)$_3$], 1.86–2.00 (m, 1H; 3′′-H_a), 2.06–2.30 (m, 3H; 3′′-H_b, 4′′-H), 2.63 (dd, *J* = 15.5, 5.4 Hz, 1H; 3′-H_a), 3.23 (dd, *J* = 15.5, 8.5 Hz, 1H; 3′-H_b), 3.68 (s, 3H; OMe), 3.71 (s, 3H; OMe), 4.41 (s, 3H; CH_3), 4.51–4.67 (m, 2H; 5′′-H), 4.77 (t, *J* = 5.9 Hz, 2H; 6-H), 4.81–4.94 (m, 1H; 2′′-H), 5.43–5.52 (m, 1H; 2′-H), 8.56 (t, *J* = 5.9 Hz, 1H; CON*H*), 8.85 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (C-4′′), 26.9 (C-3′′), 28.2 [4 × C(CH_3)$_3$], 32.6 (C-6), 37.4 (C-3′), 39.2 (CH_3), 52.6 (2 × OMe), 53.8 (C-5′′), 55.1 (C-2′), 57.0 (C-2′′), 83.8, 83.9 [3 × C(CH_3)$_3$], 130.8 (C-5), 142.9 (C-4), 151.6, 152.4 [3 × COO*t*Bu], 170.6, 170.8, 171.1 ppm (C-1′, C-4′, C-1′′); FT-IR (ATR): ṽ = 443 (w), 464 (w), 645 (w), 732 (m), 781 (w), 851 (m), 917 (w), 1001 (w), 1119 (s), 1142 (vs), 1167 (s), 1232 (s), 1314 (m), 1367 (vs), 1456 (m), 1536 (w), 1697 (s), 1743 (vs9, 1787 (m), 2980 (m), 3183 (w) cm^{-1}; MS (ESI positive): *m/z* = 771 $[M]^+$, 739, 671, 639, 571, 539, 515; HRMS (ESI positive): *m/z* calcd. for $C_{35}H_{59}N_6O_{13}^+$: 771.4135 $[M]^+$, found 771.4139; MS (ESI negative): *m/z* = 227, 216, 181, 171, 157, 143, 127 $[M]^-$, 121, 113; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9057.

4-[((S)-2-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxopropoxy)methyl]-1-((S)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (38a-MeI): From **38a** (136 mg, 0.27 mmol) in MeCN (5.00 mL), MeI (0.54 mL, 8.67 mmol), 6 d, brown solid (119 mg, 0.19 mmol, 70 %). M.p. 63 °C; $[\alpha]_D^{20}$ = –11.6 (*c* = 0.94 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 [s, 9H; C(CH_3)$_3$], 1.43 [s, 9H; C(CH_3)$_3$], 3.77 (s, 3H; OMe), 3.82 (s, 3H; OMe), 3.86–4.05 (m, 2H; 3′-H), 4.30 (s, 3H; CH_3), 4.44–4.53 (m, 1H; 2′-H), 4.75–4.87 (m, 1H; 2′′-H), 4.93 (s, 2H; 6-H), 5.05–5.30 (m, 2H; 3′′-H), 5.37 (d, *J* = 5.6 Hz, 1H; N*H*C-2′), 6.43 (d, *J* = 6.6 Hz, 1H; N*H*C-2′′), 9.15 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 28.3 [C(CH_3)$_3$], 39.6 (CH_3), 52.9 (2 × OMe), 53.4 (C-2′′), 53.7 (C-2′), 53.9 (C-3′′), 61.3 (C-6), 71.6 (C-3′), 80.3 [C(CH_3)$_3$], 80.8 [C(CH_3)$_3$], 131.6 (C-5), 139.9 (C-4), 155.3, 155.5 (2 × COO*t*Bu), 168.8, 170.6 ppm (C-1′, C-1′′); FT-IR (ATR): ṽ = 646 (w), 733 (w), 733 (w), 782 (w), 853 (w), 1027 (m), 1067 8m), 1111 (m), 1163 (vs), 1251 (s), 1305 (m), 1367 (s), 1393 (m), 1438 (m), 1510 (s), 1706 (vs), 1742 (s), 2006 (w), 2165 (w), 2978 (m), 3368 (m) cm^{-1}; MS (ESI positive): *m/z* = 516 $[M]^+$, 460, 404, 360, 337, 316, 281, 259; HRMS (ESI positive): *m/z* calcd. for $C_{22}H_{38}N_5O_9^+$: 516.2664 $[M]^+$, found 516.2662; MS (ESI negative): *m/z* = 157, 127 $[M]^-$, 113; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9054.

1-((*S*)-3-(Bis(*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl)-4-(((S)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropoxy)methyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (38b-MeI): From **38b** (189 mg, 0.31 mmol) in MeCN (5.53 mL), MeI (0.62 mL, 9.96 mmol), 6 d, orange wax (202 mg, 0.27 mmol, 87 %). $[\alpha]_D^{20}$ = +4.9° (*c* = 1.19 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43, 1.50 [2 × s, 27H; C(CH_3)$_3$], 2.44–2.58 (m, 1H; 3′′-H_a), 2.87–3.03 (m, 1H; 3′′-H_b), 3.73 (s, 3H; OMe), 3.76 (s, 3H; OMe), 3.88–3.95 (m, 1H; 3′-H_a), 3.98–4.05 (m, 1H; 3′-H_b), 4.31 (s, 3H; CH_3), 4.44–4.57 (m, 1H; NH), 4.83 (t, *J* = 6.8 Hz, 2H; 4′′-H), 4.88 (t, *J* = 6.7 Hz, 1H; 2′′-H), 5.04 (s, 2H; 6-H), 5.31–5.43 (m, 1H; 2′-H), 9.26 ppm (s, 1H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 28.4 [3 × C(CH_3)$_3$], 30.4 (C-3′′), 39.5 (CH_3), 52.1 (C-4′′), 52.8 (2 × OMe), 53.0 (C-2′), 55.1 (C-2′′), 61.5 (C-6), 71.8 (C-3′), 84.5 [3 × C(CH_3)$_3$], 131.3 (C-5), 140.3 (C-4), 152.1 (3 × COO*t*Bu), 170.7 ppm (C-1′, C-1′′); FT-IR (ATR): ṽ = 578 (w), 783 (w), 852 (w), 1117 (s), 1144 (vs), 1164 (vs), 1248 (s), 1367 (vs), 1456 (m), 1512 (m), 1705 (vs), 1744 (vs), 2024 (w), 2157 (w), 2979 (m), 3384 (w) cm^{-1}; MS (ESI positive): *m/z* = 630 $[M]^+$, 574, 530, 474, 456, 374, 315, 259; HRMS (ESI, positive): *m/z* calcd. for $C_{28}H_{48}N_5O_{11}^+$:

630.3345 $[M]^+$, found 630.3344; MS (ESI negative): *m/z* = 209, 157, 141, 127 $[M]^-$; HRMS (ESI negative): *m/z* calcd. for I^-: 126.9039 $[M]^-$, found 126.9048.

1-((*S*)-4-(Bis(*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentyl)-4-(((S)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropoxy)methyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Iodide (38c-MeI): From **38c** (190 mg, 0.30 mmol) in MeCN (5.40 mL), MeI (0.60 mL, 1.40 g, 9.6 mmol), 5 d, yellow wax (210 mg, 0.27 mmol, 90 %); R_f = 0.37 (CH_2Cl_2/MeOH, 15:1). $[\alpha]_D^{20}$ = –6.43 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 [s, 9H; C(CH_3)$_3$], 1.50 [s, 18H; 2 × C(CH_3)$_3$], 1.60–1.87 (m, 2H; 3′′-H),1.92–2.04 (m, 2H; 4′′-H), 2.12–2.27 (m, 3H; CH_3) 3.72 (s, 3H; OMe), 3.78 (s, 3H; OMe), 3.91–3.96 (m, 1H; 3′-H), 4.37–4.55 (m, 4H; 2′-H, 5′′-H), 4.74–4.80 (m, 2H; 6-H), 4.85–4.90 (m, 1H; 2′′-H), 5.31–5.38 (m, 1H; N*H*), 9.34 ppm (s, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (C-3′′), 26.5 (C-4′′), 28.0 [(2 × C(CH_3)], 28.3 [(C(CH_3)], 39.6(C-5′′), 52.4 (OMe), 52.8 (OMe), 53.7 (C-2′), 57.0 (C-2′′), 61.3 (C-6), 71.4 (C-3′), 80.2 [N(CH_3)], 83.7 [(*C*(CH_3)], 130.8 (C-4), 140.0 (C-5), 152.1 (2 × *C*OO*t*Bu), 155.3 (*C*OO*t*Bu), 170.5 ppm (C-1′, C-1′′); FT-IR (ATR): $\tilde{\nu}$ = 2979 (w), 2381 (w), 2175 (w), 2155 (w), 2003 (w), 1959 (w), 1742 (s), 1703 (s), 1507 (m), 1456 (m), 1437 (m), 1366 (m), 1309 (m), 1248 (m), 1160 (s), 1114 (s), 919 (w), 850 (m), 781 (m), 730 (m), 640 (w), 581 (w), 461 (w) cm^{-1}; MS (ESI): *m/z* = 644 $[M]^+$, 588, 544, 488, 470, 388, 259; HRMS (ESI): *m/z* calcd. for $C_{29}H_{50}N_5O_{11}^+$: 644.3493 $[M]^+$, found 644.3501.

Acknowledgments

Generous financial support by the Ministerium für Wissenschaft, Forschung und Kunst des Landes Baden-Württemberg, the Carl-Zeiss-Stiftung (Projecthouse NanoBioMater), the Forschungsfonds der Universität Stuttgart, the Baden-Württemberg-Stiftung (project BioMat-S11 BiogelPlus) and the Alfred-Kärcher-Stiftung are gratefully acknowledged. Open access funding enabled and organized by Projekt DEAL.

Keywords: Amino acids · Biological activity · Click chemistry · Triazoles · Triazolium

[1] a) A. Rani, G. Singh, A. Singh, U. Maqbool, G. Kaur, J. Singh, *RSC Adv.* **2020**, *10*, 5610–5635; b) K. Bozorov, J. Zhao, H. A. Aisa, *Bioorg. Med. Chem.* **2019**, *27*, 3511–3531; c) N. I. Korotkikh, A. H. Cowley, J. A. C. Clyburne, K. N. Robertson, V. S. Saberov, N. V. Glinyanaya, G. F. Rayenko, O. P. Shvaika, *ARKIVOC* **2017**, *2017*, 257–355; d) G. Guisado-Barrios, M. Soleilhavoup, G. Bertrand, *Acc. Chem. Res.* **2018**, *51*, 3236–3244; e) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann, M. W. Paixao, *Chem. Commun.* **2015**, *51*, 10784–10796; f) J.-P. Wan, D. Hu, Y. Liu, S. Sheng, *ChemCatChem* **2015**, *7*, 901–903; g) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696–2718; h) M. Juricek, P. H. J. Kouwer, A. E. Rowan, *Chem. Commun.* **2011**, *47*, 8740–8749; i) A. Dondoni, *Org. Biomol. Chem.* **2010**, *8*, 3366–3385; j) D. Dheer, V. Singh, R. Shankar, *Bioorg. Chem.* **2017**, *71*, 30–54; k) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A. M. Almerico, *Eur. J. Org. Chem.* **2014**, *2014*, 3289–3306; l) I. E. Valverde, T. L. Mindt, *Chimia* **2013**, *67*, 262–266; m) I. Pibiri, S. Buscemi, *Curr. Bioactive Compd.* **2010**, *6*, 208–242; n) See ref.[1b].

[2] J. M. Aizpurua, R. M. Fratila, Z. Monasterio, N. Pérez-Esnaola, E. Andreieff, A. Irastorza, M. Sagartzazu-Aizpurua, *New J. Chem.* **2014**, *38*, 474–480.

[3] a) J. C. Slootweg, S. van der Wal, H. C. Quarles van Ufford, E. Breukink, R. M. J. Liskamp, D. T. S. Rijkers, *Bioconjugate Chem.* **2013**, *24*, 2058–2066; b) C. Li, J. Tang, J. Xie, *Tetrahedron* **2009**, *65*, 7935–7941; c) F. M. Mir, N. D. P. Atmuri, C. B. Bourguet, J. R. Fores, X. Hou, S. Chemtob, W. D. Lubell, *J. Med. Chem.* **2019**, *62*, 4500–4525; d) K. Maji, M. Abbasi, D. Podder, R. Datta, D. Haldar, *ChemistrySelect* **2018**, *3*, 10220–10225; e) G. Silveira-Dorta, S. Jana, L. Borkova, J. Thomas, W. Dehaen, *Org. Biomol. Chem.* **2018**, *16*, 3168–3176; f) S. Malkowski, C. Dishuck, G. Lamanilao, C. Embry, C. Grubb, M. Cafiero, L. Peterson, *Molecules* **2017**, *22*, 1682–1695; g) S. N. S. Vasconcelos, E. Fornari, I. Caracelli, H. A. Stefani, *Mol. Diversity* **2017**, *21*, 893–902; h) L. R. Yule, R. L. Bower, H. Kaur, R. Kowalczyk, D. L. Hay, M. A. Brimble, *Org. Biomol. Chem.* **2016**, *14*, 5238–5245; i) S. M. Wales, K. A. Hammer, A. M. King, A. J. Tague, D. Lyras, T. V. Riley, P. A. Keller, S. G. Pyne, *Org. Biomol. Chem.* **2015**, *13*, 5743–5756; j) J.-P. Huo, J.-C. Luo, W. Wu, J.-F. Xiong, G.-Z. Mo, Z.-Y. Wang, *Ind. Eng. Chem. Res.* **2013**, *52*, 11850–11857; k) J. Huo, M. Lü, Z. Wang, Y. Li, *Chin. J. Chem.* **2012**, *30*, 2411–2422; l) C. Proulx, W. D. Lubell, *J. Org. Chem.* **2010**, *75*, 5385–5387; m) M. Klein, K. Krainz, I. N. Redwan, P. Dinér, M. Grøtli, *Molecules* **2009**, *14*, 5124–5143; n) N. G. Angelo, P. S. Arora, *J. Org. Chem.* **2007**, *72*, 7963–7967; o) N. G. Angelo, P. S. Arora, *J. Am. Chem. Soc.* **2005**, *127*, 17134–17135; p) J. F. Billing, U. J. Nilsson, *J. Org. Chem.* **2005**, *70*, 4847–4850.

[4] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, *Farmaco* **1996**, *51*, 301–303.

[5] a) S. D. Whedon, M. K. Parker, E. L. Tyson, T. Ritterhoff, P. M. M. Shelton, C. Chatterjee, *Chem. Commun.* **2019**, *55*, 2043–2045; b) M. Bauer, W. Wang, M. M. Lorion, C. Dong, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 203–207; *Angew. Chem.* **2018**, *130*, 209–213; c) A. M. Beekman, M. A. O'Connell, L. A. Howell, *Angew. Chem. Int. Ed.* **2017**, *56*, 10446–10450; *Angew. Chem.* **2017**, *129*, 10582; d) E. Oueis, M. Jaspars, N. J. Westwood, J. H. Naismith, *Angew. Chem. Int. Ed.* **2016**, *55*, 5842–5845; *Angew. Chem.* **2016**, *128*, 5936; e) W. S. Horne, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **2003**, *125*, 9372–9376; f) C. T. Walsh, S. Garneau-Tsodikova, G. J. Gatto, *Angew. Chem. Int. Ed.* **2005**, *44*, 7342–7372; *Angew. Chem.* **2005**, *117*, 7508.

[6] a) H. Fu, P.-X. Shen, J. He, F. Zhang, S. Li, P. Wang, T. Liu, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 1873–1876; *Angew. Chem.* **2017**, *129*, 1899; b) K. K. H. Vong, S. Maeda, K. Tanaka, *Chem. Eur. J.* **2016**, *22*, 18865–18872.

[7] a) Z. Benfodda, D. Benimélis, G. Reginato, P. Meffre, *Amino Acids* **2018**, *50*, 1307–1328; b) T. Boibessot, D. Bénimélis, P. Meffre, Z. Benfodda, *Amino Acids* **2016**, *48*, 2081–2101; c) Z. Benfodda, D. Bénimélis, M. Jean, J.-V. Naubron, V. Rolland, P. Meffre, *Amino Acids* **2015**, *47*, 899–907; d) Z. Benfodda, D. Bénimélis, G. Reginato, P. Meffre, *Amino Acids* **2015**, *47*, 271–279; e) G. Reginato, P. Meffre, F. Gaggini, *Amino Acids* **2005**, *29*, 81–87; f) P. Meffre, S. Hermann, P. Durand, G. Reginato, A. Riu, *Tetrahedron* **2002**, *58*, 5159–5162.

[8] a) Y. Koseki, T. Sugimura, K. Ogawa, R. Suzuki, H. Yamada, N. Suzuki, Y. Masuyama, Y. Y. Lin, T. Usuki, *Eur. J. Org. Chem.* **2015**, *2015*, 4024–4032; b) Y. Murakami, R. Suzuki, H. Yanuma, J. He, S. Ma, G. M. Turino, Y. Y. Lin, T. Usuki, *Org. Biomol. Chem.* **2014**, *12*, 9887–9894.

[9] J. A. Marchand, M. E. Neugebauer, M. C. Ing, C.-I. Lin, J. G. Pelton, M. C. Y. Chang, *Nature* **2019**, *567*, 420–424.

[10] a) S. F. Yan, R. Ramasamy, A. M. Schmidt, *Nat. Clin. Pract. Endocrinol. Metab.* **2008**, *4*, 285–293; b) H. Yamada, T. Sasaki, S. Niwa, T. Oishi, M. Murata, T. Kawakami, S. Aimoto, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5677–5680; c) R. Singh, A. Barden, T. Mori, L. Beilin, *Diabetologia* **2001**, *44*, 129–146.

[11] a) B. Sheng, L. Larsen, T. Le, D. Zhao, *Molecules* **2018**, *23*, 712–723; b) H. Kaur, M. Kamalov, M. A. Brimble, *Acc. Chem. Res.* **2016**, *49*, 2199–2208; c) Y. Nomi, H. Annaka, S. Sato, E. Ueta, T. Ohkura, K. Yamamoto, S. Homma, E. Suzuki, Y. Otsuka, *J. Agric. Food Chem.* **2016**, *64*, 8397–8405; d) M. O. Lederer, R. G. Klaiber, *Bioorg. Med. Chem.* **1999**, *7*, 2499–2507; e) U. Moeckel, A. Duerasch, A. Weiz, M. Ruck, T. Henle, *J. Agric. Food Chem.* **2016**, *64*, 2953–2961.

[12] a) K. M. Biemel, D. A. Friedl, M. O. Lederer, *J. Biol. Chem.* **2002**, *277*, 24907–24915; b) K. M. Biemel, O. Reihl, J. Conrad, M. O. Lederer, in *Int. Congr. Ser.*, Elsevier, **2002**, pp. 255–261; c) O. Reihl, K. M. Biemel, W. Eipper, M. O. Lederer, W. Schwack, *J. Agric. Food Chem.* **2003**, *51*, 4810–4818; d) S. M. Culbertson, E. I. Vassilenko, L. D. Morrison, K. U. Ingold, *J. Biol. Chem.* **2003**, *278*, 38384–38394; e) D. R. Sell, K. M. Biemel, O. Reihl, M. O. Lederer, C. M. Strauch, V. M. Monnier, *J. Biol. Chem.* **2005**, *280*, 12310–12315; f) G. Ravichandran, D. K. Lakshmanan, K. Raju, A. Elangovan, G. Nambirajan, A. A. Devanesan, S. Thilagar, *Environ. Int.* **2019**, *123*, 486–500.

[13] a) M. O. Lederer, F. Gerum, T. Severin, *Bioorg. Med. Chem.* **1998**, *6*, 993–1002; b) M. O. Lederer, H. P. Bühler, *Bioorg. Med. Chem.* **1999**, *7*, 1081–1088; c) See ref.[11d]; d) K. M. Biemel, O. Reihl, J. Conrad, M. O. Lederer, *J. Biol. Chem.* **2001**, *276*, 23405–23412; e) K. M. Biemel, J. Conrad, M. O.

Lederer, *Angew. Chem. Int. Ed.* **2002**, *41*, 801–804; *Angew. Chem.* **2002**, *114*, 826; f) O. Reihl, M. O. Lederer, W. Schwack, *Carbohydr. Res.* **2004**, *339*, 483–491.

[14] V. R. Sabbasani, K.-P. Wang, M. D. Streeter, D. A. Spiegel, *Angew. Chem. Int. Ed.* **2019**, *58*, 18913–18917; *Angew. Chem.* **2019**, *131*, 19089.

[15] a) A. Bettiga, F. Fiorio, F. Di Marco, F. Trevisani, A. Romani, E. Porrini, A. Salonia, F. Montorsi, R. Vago, *Nutrients* **2019**, *11*, 1748–1766; doi https://doi.org/10.3390/nu11081748; b) M. Friedman, *J. Agric. Food Chem.* **1996**, *44*, 631–653; c) V. M. Monnier, G. T. Mustata, K. L. Biemel, O. Reihl, M. O. Lederer, D. Zhenyu, D. R. Sell, *Ann. N. Y. Acad. Sci.* **2005**, *1043*, 533–544; d) X. Fan, D. R. Sell, J. Zhang, I. Nemet, M. Theves, J. Lu, C. Strauch, M. K. Halushka, V. M. Monnier, *Free Radical Biol. Med.* **2010**, *49*, 847–856; e) M. W. Poulsen, R. V. Hedegaard, J. M. Andersen, B. de Courten, S. Bügel, J. Nielsen, L. H. Skibsted, L. O. Dragsted, *Food Chem. Toxicol.* **2013**, *60*, 10–37; f) V. M. Monnier, W. Sun, D. R. Sell, X. Fan, I. Nemet, S. Genuth, *Clin. Chem. Lab. Med.* **2014**, *52*, doi https://doi.org/10.1515/cclm-2013 0174; g) M. Hellwig, T. Henle, *Angew. Chem. Int. Ed.* **2014**, *53*, 10316–10329; *Angew. Chem.* **2014**, *126*, 10482.

[16] J. M. Padrón, G. Kokotos, T. Martín, T. Markidis, W. A. Gibbons, V. S. Martín, *Tetrahedron: Asymmetry* **1998**, *9*, 3381–3394.

[17] M. Adamczyk, D. D. Johnson, R. E. Reddy, *Tetrahedron: Asymmetry* **2000**, *11*, 3063–3068.

[18] M. Biel, P. Deck, A. Giannis, H. Waldmann, *Chem. Eur. J.* **2006**, *12*, 4121–4143.

[19] Y. Koseki, H. Yamada, T. Usuki, *Tetrahedron: Asymmetry* **2011**, *22*, 580–586.

[20] S. Roth, N. R. Thomas, *Synlett* **2010**, *4*, 607–609.

[21] M. S. Martini, Dissertation, Universität Stuttgart, **2015**.

[22] G. Pavé, S. Usse-Versluys, M.-C. Viaud-Massuard, G. Guillaumet, *Org. Lett.* **2003**, *5*, 4253–4256.

[23] D. Shetty, J. M. Jeong, C. H. Ju, Y. J. Kim, J.-Y. Lee, Y.-S. Lee, D. S. Lee, J.-K. Chung, M. C. Lee, *Bioorg. Med. Chem.* **2010**, *18*, 7338–7347.

[24] T. Boibessot, D. Bénimélis, M. Jean, Z. Benfodda, P. Meffre, *Synlett* **2016**, *27*, 2685–2688.

[25] E. Fenster, C. Fehl, J. Aubé, *Org. Lett.* **2011**, *13*, 2614–2617.

[26] L. Bondarenko, I. Dix, H. Hinrichs, H. Hopf, *Synthesis* **2004**, *16*, 2751–2759.

[27] See ref.[7f].

[28] M. Jiang, H. Yang, H. Fu, *Org. Lett.* **2016**, *18*, 1968–1971.

[29] V. Haridas, Y. K. Sharma, S. Sahu, R. P. Verma, S. Sadanandan, B. G. Kacheshwar, *Tetrahedron* **2011**, *67*, 1873–1884.

[30] S. Chakraborty, D. Tai, *Tetrahedron Lett.* **2014**, *55*, 2274–2276.

[31] S. Ballet, C. Betti, A. Novoa, C. Tömböly, C. Uhd Nielsen, H. C. Helms, A. Lesniak, P. Kleczkowska, N. N. Chung, A. W. Lipkowski, B. Brodin, D. Tourwe, P. W. Schiller, *ACS Med. Chem. Lett.* **2014**, *5*, 352–357.

[32] Z.-L. Wei, P. A. Petukhov, F. Bizik, J. C. Teixeira, M. Mercola, E. A. Volpe, R. I. Glazer, T. M. Willson, A. P. Kozikowski, *J. Am. Chem. Soc.* **2004**, *126*, 16714–16715.

[33] See ref.[3b].

[34] A. Flores, M. J. Camarasa, M. J. Pérez-Pérez, A. San-Félix, J. Balzarini, E. Quesada, *Org. Biomol. Chem.* **2014**, *12*, 5278–5294.

[35] B. Adhikari, G. Palui, A. Banerje, *Soft Matter* **2009**, *5*, 3452–3460.

[36] J. E. M. N. Klein, M. Holzwarth, S. Hohloch, B. Sarkar, B. Plietker, *Eur. J. Org. Chem.* **2013**, 6310–6316.

[37] Bio-Rad, "alamarBlueR - Cell Viability Assay," can be found under https://www.bio-rad-antibodies.com/alamarblue-cell-viability-assayresazurin.html, **2019**.

[38] R. S. Meinel, A. das Chagas Almeida, P. H. Fazza Stoppa, N. Glanzmann, E. S. Coimbra, A. D. da Silva, *Chem.-Biol. Interact.* **2020**, *315*, 108850–108856.

Received: June 8, 2020

